CLINICAL PRACTICE IN INFECTIOUS DISEASES

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For Students, Practitioners and Medical Officers

BY

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THIS BOOK

IS

DEDICATED TO OUR FORMER

CHIEF

SIR FREDERICK MENZIES

K.B.E., K.H.P., LL.D., M.D., F.R.C.P.

Made and Printed in Great Britain

AUTHORS' PREFACE

This book is an elaboration of notes on clinical lectures delivered to students of London Medical Schools at the North-eastern and Eastern Hospitals of the London County Council and to Birmingham University students at the City Hospital, Little Bromwich. It is intended to provide an account of the clinical aspects of the acute specific infectious diseases sufficiently full for the needs of the student, the practitioner and the medical officer in the public health service. Although, in the main, the book represents the personal experience of the authors as clinicians, teachers and examiners, an endeavour has been made to set out modern fever practice as reflected in the work of others. The preliminary chapters, dealing with such topics as the sources and modes of infection, resistance, allergy, general management, diet, rashes, laboratory aids and clinical tests, provide a broad basis for the whole subject and obviate repetition in later chapters by the provision of numerous cross-references.

Since many students attend their course in fevers early in their clinical period, this preliminary section has been written from first principles and with due regard to the importance of regarding "fevers" as a branch of medicine in general, and of pædiatrics in particular. The student is strongly urged to master this section before proceeding to the chapters treating of individual diseases.

These are grouped primarily into inhalation and ingestion diseases. Hæmolytic streptococcal fevers and epidemic diseases of the nervous system form separate sub-groups, each preceded by a description of the features common to the group. The ingestion diseases are similarly introduced. Certain diseases likely to assume increased importance under war conditions have been included, *e.g.*, Weil's disease, the louse-borne infections (epidemic typhus, trench fever and epidemic relapsing fever), epidemic influenza and tetanus. Prophylaxis has been emphasised throughout, and the control of infectious diseases in hospital is described fully in a terminal chapter.

Illustrations of the exanthemata in half-tone, or even in colour plates—unless the latter are reproduced by the most

expensive processes—are rarely of any value to the student. On the contrary, they may give impressions which are entirely misleading. The authors have considered it more useful to restrict illustrations to simple line and coloured diagrams. Numerous original papers have been drawn upon, the name of the author and the date of publication being stated in the text. It is debatable, however, whether in a book intended largely for students the provision of lists of references is desirable. The authors have taken the view that, for the clinical student, the space is more profitably occupied by synoptic tables and by brief summaries of the contents of the chapters.

We acknowledge with gratitude our indebtedness to Sir Frederick Menzies for his permission to use the records of patients and to draw freely upon reports of Departmental Committees of the London County Council on which one or both the authors have served. We would also express our thanks to the Editor of *The Lancet* for permission to reproduce the electrocardiograms and diagrams in the chapter on Diphtheria; to the Editors of *The Practitioner* for allowing full quotation of matter contributed by one of us in the chapter on Diet in Infectious Diseases; to Dr N. D. Begg for his consent to the use of his electrocardiograms; and to Lieutenant B. J. Harries, R.A.M.C., for his assistance in the preparation of the index.

Dr J. A. H. Brincker, until recently Principal Medical Officer of the Special Hospitals Division of the Public Health Department, London County Council, has given unfailing encouragement and assistance in the preparation of the book, which, in great measure, records the practice of the infectious diseases hospitals under his immediate control.

We would also express our appreciation of the patience of our publishers and of their constant endeavour to carry out any suggestions.

E. H. R. HARRIES
M. MITMAN

LONDON,
1940.

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FOREWORD

The publication of a new textbook on infectious diseases is welcome.

During recent years there has been a substantial increase in our knowledge of the prevention and treatment of these diseases. This new knowledge is scattered through the pages of the medical periodicals, annual and other reports of Public Health Departments, central and local, and of the Medical Research Council.

Dr Harries and Dr Mitman have not only gathered all this material together, but they have been quick to test in their own hospitals any new idea which promised success. This textbook includes, therefore, a critical commentary on the practical application of recent advances in the field of endeavour known as "fever work." There is now intense activity in this field. For a period of two or three decades from the bringing into use of antidiphtheritic serum there was no striking discovery of value to those engaged in infectious diseases work. Then came a burst of research, the result of which has revolutionised fever hospital practice. Examples crowd upon the mind, but it will suffice to mention: Schick testing and immunisation against diphtheria, Dick testing and the use of serum for the treatment of scarlet fever, the typing of *Streptococcus hæmolyticus* and proof of reinfection by differing types, the use of sulphonamide preparations for therapeutic purposes, and the use of measles serum for prophylaxis. Dr Harries and Dr Mitman have provided a textbook which deals not only with "recent advances," but which covers the whole ground. First principles are emphasised, present theory and practice are described fully, and the reader is not wearied by descriptions of methods now discarded.

The book should appeal to a wide circle. To the doctor in busy general practice this book will, with the minimum of verbiage, tell him what has been discovered about fevers in

recent years. To the medical student it provides adequate knowledge for a qualifying examination and a sound foundation for clinical practice. To the D.P.H. student it sets out in modest compass all that is needed as a complement to clinical instruction in the wards. To the Fever Hospital Resident and Medical Officer of Health it brings to mind and collates all that he has read in the last few years of the most recent phases of fever work.

I have great pleasure in complimenting the authors on the successful conclusion of a most useful piece of work and in wishing the volume the success which it deserves.

W. ALLEN DALEY

Clinical Practice in Infectious Diseases

CHAPTER I

INFECTIOUS DISEASES: NOTIFICATION

ALL diseases *communicable* from one human being to another, or from an animal to a human being, are, in the widest sense of the term, *infectious*. The transmission of such diseases is possible because the causal agents are living parasites. Thus there is no fundamental difference between the diseases commonly classed as "infectious" and the rest of the medical and surgical diseases due to living agents. In practice, however, the term *infectious diseases* is limited to those which are most readily transmissible, the term *infective* being used for all diseases due to living agents. The infectious diseases are so readily transmissible that a large number of persons may be affected in more or less rapid succession by an identical or similar symptom-complex, so giving rise to an *epidemic*, *e.g.*, of measles. The fact that an epidemic of a given infectious disease may occur implies that the causal agent is *specific* for that disease, and therefore the term *acute specific infectious diseases* is sometimes applied to the conditions described in this book. But with increasing knowledge it becomes evident that the identical causal agent may, in some instances, give rise to diverse clinical conditions. This is particularly the case in hæmolytic streptococcal infections. Scarlet fever, for example, is a streptococcal infection of the fauces typically associated with a rash, and is invariably classed as an infectious disease; acute streptococcal tonsillitis, an infection of the fauces, is not usually regarded as an infectious disease; and acute streptococcal appendicitis is never so regarded. Yet the same strain of the streptococcus may be responsible and may enter the body in the same way in all three diseases. Again, the virus causal of chickenpox may give rise to herpes zoster, and the patient so attacked may initiate an outbreak of chickenpox. Generally speaking, however, the acute specific

infectious diseases "breed true" and on transmission cause conditions recognisable as the same clinical entities.

An artificial distinction used to be drawn between diseases transmissible through the air, called *infectious*, and those which could only be transmitted by direct contact, called *contagious*. It is now known that many diseases can be conveyed by both methods. Moreover, the old conception of infectious diseases being air-borne over long distances is incorrect. Infection of the air almost always depends upon the presence in it of minute infected droplets of mucus expelled from the nose and throat of an infected person. The range of these droplets is seldom more than a few feet; beyond this range infection through the air rarely takes place.

A term now almost obsolete is *zymotic diseases*. Infectious diseases were so called because the processes responsible for them were regarded as resembling fermentation. The term still lingers in *zymotic enteritis*.

Formerly a distinction was drawn between diseases with a rash, the *exanthemata*, and those without. The division is fallacious because the same disease may occur with or without a rash, which is only one element of the symptom-complex.

Most acute infections cause a rise in the body temperature —pyrexia or fever—which is usually accompanied by general symptoms such as headache, malaise, nausea and vomiting. As these disturbances are common in the infectious diseases they are sometimes classed as *fevers*. Pyrexia, however, is not a constant symptom and some of the most severe attacks of infectious disease may be apyrexial.

Notifiable Diseases.—The Medical Officer of Health of a district must be notified of the occurrence of certain infectious diseases, and the law relating to this is summarised below. The diseases which were originally made notifiable were the more serious ones, but this distinction is not always accurate. Scarlet fever, a notifiable disease, was once a serious condition, but has changed its form and is now relatively mild. On the other hand, measles, which until recently was not notifiable, was considered a trivial ailment but is now recognised to be a serious disease. Moreover, some of the notifiable diseases, *e.g.*, cholera, although occasionally introduced from abroad, are extinct in this country and possess little public health significance, whereas non-notifiable diseases like influenza, the common cold and tonsillitis are of considerable national importance. The distinction between notifiable and non-notifiable disease is therefore artificial.

The object of compulsory notification was to permit the

prompt isolation of the more serious diseases, either in the house if conditions permitted or in isolation hospitals. It was believed that isolation would check the spread and so eliminate the disease from the community, but owing to the occurrence of carriers, missed cases and abortive cases these measures have proved unsuccessful. Nevertheless, notification by keeping the authorities informed of the prevalence of any particular infectious disease enables prompt application of appropriate prophylactic and therapeutic measures; further, notifiable diseases are regarded with respect by the laity, whereas a non-notifiable condition is apt to be regarded as trivial—with unfortunate results in many cases.

The Law Relating to Infectious Diseases.—The laws relating to infectious diseases are contained mainly in the **Public Health Act, 1936,** and in **Regulations** made by powers conferred under various Acts. No attempt is made to define infectious diseases, but the Act of 1936 contains a list of *notifiable diseases*. Certain of these are classed as *dangerous infectious diseases* requiring more rigid measures of control than others not so included.

1. Diseases which require to be notified because they are *notifiable diseases* under the Public Health Act of 1936:—

   Smallpox.
   Cholera.
   Diphtheria.
   Membranous Croup.
   Erysipelas.
   Scarlet Fever.
   Fevers known by any of the following names: Typhus, Typhoid, Enteric, Relapsing.

2. Diseases which require to be notified under Public Health *Regulations or Orders*:—

   Plague.
   Tuberculosis.
   Acute Poliomyelitis.
   Acute Polioencephalitis.
   Cerebrospinal Fever.
   Ophthalmia Neonatorum.
   Puerperal Pyrexia.
   Malaria.
   Dysentery.
   Acute Primary Pneumonia.
   Acute Influenzal Pneumonia.

3. Diseases which in special circumstances *may* be made notifiable :—

   The local authority may order, subject to the approval of the Minister of Health, that other diseases shall be notifiable. The local authority will give notice in local newspapers and to medical practitioners in the district of their intention to do so. These additional diseases are usually made notifiable during epidemics and for a limited period. Chickenpox, for example, is sometimes made notifiable when smallpox is prevalent in an endeavour to avoid overlooking cases of smallpox misdiagnosed as chickenpox. The diseases most commonly added to the list of notifiable diseases are rubella, chickenpox, zymotic enteritis and diarrhœa. Measles and whooping-cough have recently been added to the list of notifiable diseases by the Ministry of Health.

Notification.—The law requires that—

1. The head of the family must notify the Medical Officer of Health of the district as soon as he becomes aware that a member of his household is suffering from a notifiable disease. (Failing the head of the family, notification must be made by a near relative, attendant or the occupier of the building.)
2. Every medical practitioner in attendance must likewise notify the Medical Officer of Health. The fine in default is 40s.

The local authority (Public Health Department) will, on application, supply medical practitioners free of charge, with forms of certificates, and will pay for each certificate :—

(*a*) A fee of 2s. 6d. if the case occurs in his private practice ;
(*b*) A fee of 1s. if the case occurs in his practice as medical officer of any public body or institution.

Exposure of Persons and Articles.—To avoid exposing others to the risk of infection, restrictions are imposed on persons and articles liable to convey infection. A person suffering from a dangerous infectious disease must not, by his presence or conduct in streets, public places, schools, shops, hotels, etc., or at his work, expose others to the risk of infection. He must not travel in a public conveyance in which passengers pay

separate fares (*e.g.*, in buses, trains, tubes, etc.), and can only be carried in other public conveyances, such as taxi-cabs, with the consent of the owner or driver. The Medical Officer of Health must be informed afterwards, and the vehicle must be disinfected.

Articles belonging to a person suffering from a dangerous infectious disease must not be dealt with or disposed of in such a way that they expose others to the risk of infection, *e.g.*, they must not be sold, thrown in the dustbin, sent to the laundry or cleaners, until they have been disinfected. Rooms and articles will usually be disinfected free of charge by the Medical Officer of Health.

Persons suffering from dangerous infectious diseases must not take books from circulating or public libraries, and must not return any borrowed books until they have been disinfected.

Hospital Facilities.—Public Health Authorities provide hospital accommodation for infectious diseases and may recover from persons legally liable the expenses of maintenance of patients, although usually no charge is made.

Public Health Authorities are not *compelled* to take in every case of a notifiable disease. Sometimes the Medical Officer of Health decides to leave certain types of case at home.

A Justice of the Peace may order the compulsory removal to hospital of a person suffering from a dangerous infectious disease if precautions to prevent the spread of infection cannot be taken at home.

If a patient suffering from a dangerous infectious disease dies in hospital, the Medical Officer of Health or the medical officer of the hospital may certify that the body should not be removed except for burial or cremation, *i.e.*, the body must not be taken home.

It is forbidden to hold wakes over bodies of those who have died of a notifiable disease.

Other Facilities.—Public Health Authorities usually provide laboratory facilities for the making of bacteriological, chemical and other investigations. Some provide nurses for attendance in the home on *infectious* diseases, *e.g.*, for the home care of cases of measles. Most Public Health Authorities have schemes for the immunisation of susceptible children against diseases like diphtheria, and some provide therapeutic sera.

Ambulances are also provided for the removal of patients to hospital.

SUMMARY OF CHAPTER I

Infectious Diseases: An ill-defined group of diseases due to living micro-organisms whose characteristic feature is the ease with which they can be transmitted from one human being to another.

Notifiable Diseases: A legal term for certain infectious diseases which require to be notified to the Medical Officer of Health. Certain of these are classed as *dangerous infectious diseases.*

CHAPTER II

INFECTION AND RESISTANCE

OF the living agents causal of infectious diseases, viz., bacteria, filterable viruses, fungi, protozoa and metazoa, the first two are responsible for nearly all those met with in this country.

The human host, constantly exposed to various potential parasites, defends itself by means of a complicated protective mechanism, the efficiency of which varies with the individual.

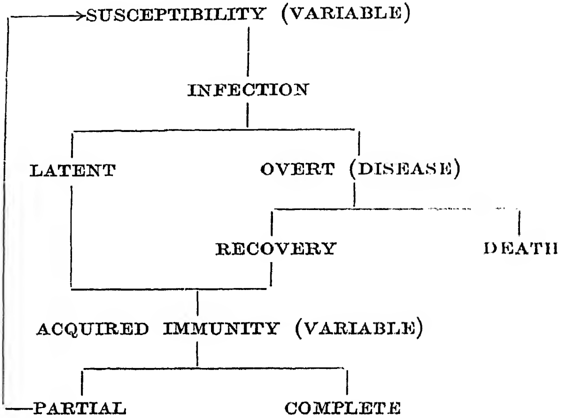
Infection.—The implantation and growth of organisms upon the tissues of the host constitutes *infection* which, however, is not necessarily followed by *disease*; the resistance of the host may entirely overcome the infection.

In relation to any given infectious disease individuals may be divided into *susceptibles* and *immunes*, it being understood that these terms are relative and not absolute; thus the same person may be able to withstand a mild infection but be incapable of dealing with a more severe one.

In some diseases it is possible by means of immunological tests to distinguish with considerable accuracy between susceptibles and immunes, *e.g.*, the Schick test in the case of diphtheria.

Results of Infection.—In the susceptible subject two possible results may follow an infection depending upon (i) the intensity of infection and (ii) the activity of the defence mechanism. If the intensity of infection is slight and the defence active, no clinical signs of illness arise although tissue changes tending to immunity take place; the infection remains *latent* or *silent*. A series of latent infections results in the mobilisation of the defence forces and the acquirement of immunity without *patent* or *overt* illness. On the other hand, if the intensity of the infection is sufficiently great to overcome the resistance an overt infection occurs and the subject suffers a clinical attack of the *disease*, the results of which may be (i) death or (ii) recovery with the attainment of active immunity identical in type with that acquired by repeated latent infections.

Relationship between Susceptibility, Infection, Disease and Acquired Immunity



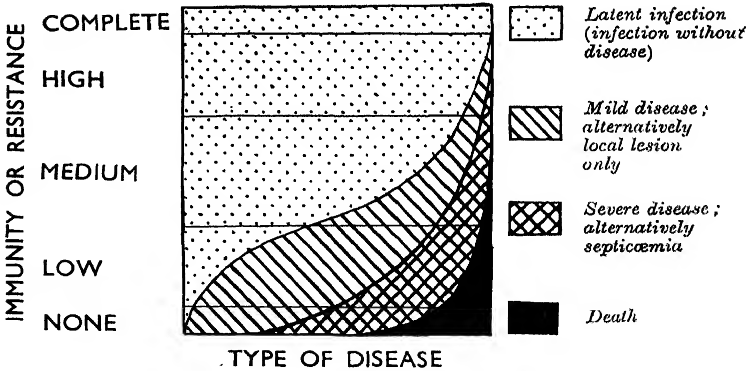


FIG. 1.—To illustrate how Resistance modifies the Effect of Infection. The diagram is schematic and has no reference to any particular disease.

When an immune individual is infected the invading organisms are, as a rule, rapidly destroyed. Occasionally the body finds it difficult to eliminate the organisms which, although incapable of producing an overt infection, continue to live and multiply within limits. This *carrier state* may persist for days, months or years. Another variety of carrier is the convalescent patient who occasionally fails to eliminate the organisms,

although, clinically, he has recovered from the disease. Carriers of some organisms, such as diphtheria bacilli, are common; of others such as tubercle bacilli, rare or non-existent.

Factors Influencing Intensity of Infection.—(i) *Species.* Of the organisms capable of infecting man—the human pathogens —some, *e.g.*, the viruses of chickenpox or rubella, are benign and rarely produce serious symptoms; others, *e.g.*, the organisms causal of cerebrospinal fever or enteric fever, frequently cause death.

(ii) *Virulence.* Different strains of the same organism vary in virulence, *i.e.*, in their capacity to injure the body. For example, diphtheria bacilli may be virulent or non-virulent, and among the virulent strains some, the *gravis* strains, tend to cause severe attacks of diphtheria, whereas others, the *mitis* strains, are more commonly associated with milder attacks.

(iii) *Velocity of Infection.* Sheldon F. Dudley (*Medical Res. Coun. Spec. Rep.*, Series No. 111, 1926) shows that "the quantitative factors of time, mass of infective agent and degree of host resistance make it essential to introduce three 'velocities' into the study of infection:—

"(*a*) The velocity at which the infective material is received by the host.

"(*b*) The velocity at which it is destroyed by the host.

"(*c*) The velocity at which the host resistance acts in a positive or negative direction.

"The resultant of these three is the 'velocity of infection' on whose magnitude depends the final result of the reaction between the host and the dependent organism. This result may be an illness mild or severe, the establishment of tolerance (*i.e.*, commensalism or the carrier state), or the destruction of the parasite; and in all cases there will be change in the host's defensive mechanism, for better or worse."

Factors Influencing Resistance. — "Resistance" and "immunity" are synonymous terms, but whereas the former implies the whole of the defensive forces of the body, the latter is sometimes used in a narrower sense and is therefore a less suitable term.

(i) *Innate Resistance.*—Resistance to some organisms may be innate and such inborn resistance may be confined to certain individuals or certain races.

(ii) *Infantile Resistance* to those acute specific infections to which the mother herself is immune is conferred through the placenta or in the milk. Such passive resistance is valid

only for the first few months of life, gradually disappearing and leaving the child susceptible.

(iii) *Acquired Resistance* results from latent or overt infections (*vide supra*). The specific protective substances, once acquired, persist in the blood and tissues and constitute a permanent defence. Thus *second attacks* of most of the specific infectious diseases are rare.

(iv) *Primary and Secondary Stimuli*.—The first infection is a *primary stimulus*, which provokes some degree of *basal immunity* and sensitises the protective mechanism so that subsequent identical infections, *secondary stimuli*, produce an accelerated response and greatly enhanced immunity.

TABLE I

ANTIGENS USED FOR ACTIVE IMMUNISATION

Type of Antigen	Examples of Active Immunisation
UNALTERED ORGANISM .	(USED ONLY IN ANIMALS).
ATTENUATED, BUT LIVING ORGANISM	VACCINATION * AGAINST SMALL-POX (VIRUS MODIFIED BY PASSAGE THROUGH CALF). INOCULATION AGAINST RABIES (VIRUS MODIFIED BY DRYING).
KILLED ORGANISM (VACCINE *)	INOCULATION AGAINST ENTERIC FEVER (T.A.B.). IMMUNISATION AGAINST WHOOPING-COUGH. VACCINES FOR COLDS, ETC.
TOXIN	IMMUNISATION AGAINST SCARLET FEVER.
MODIFIED TOXIN (TOXOID)	IMMUNISATION AGAINST DIPHTHERIA.

* *N.B.*—The term *vaccination* is usually restricted in this country to active immunisation against smallpox, for which a *vaccine* is *not* used.

(v) *Artificial Immunity.*—By artificially stimulating the mechanism of resistance to the production of specific protective substances, lasting *active immunity* may be produced ; or these protective substances may be supplied ready-made, thus conferring temporary *passive immunity.*

Active Immunisation.—Bacteria and their toxins are *antigens.* They stimulate the production of *antibodies* which counteract the effect of antigens. In active immunisation the natural process is reproduced by injecting small doses of the appropriate antigen. The use of the unmodified living organism as an antigen would be dangerous, but fortunately the organism or its products can be so modified that whilst no longer dangerous the antigenic power is retained. Some examples of antigens used in active immunisation are given in Table I.

Passive Immunisation.—In passive immunisation the subject receives *antibodies.* These are obtained from some other immune individual, or from an animal, usually the horse, which has been actively immunised. The animal is bled and the serum separated. Passive immunisation therefore involves the injection of *immune sera.* It is important to realise that foreign sera contain substances which may provoke reactions in susceptible individuals (see Serum Disease, p. 18). Examples of immune sera and the sources from which they are obtained are given in Table II.

Indications for Active or Passive Immunisation.—Passive immunity is conferred almost immediately after the injection of the serum, but is of short duration and cannot be depended upon for more than a fortnight. Active immunity takes weeks, sometimes months, to develop and usually requires the injection of more than one dose of the antigen. Once active immunity has appeared it persists for years, sometimes for the rest of the patient's life although at a lower level. The practical implication is obvious. Passive immunisation should be reserved for those who are in *immediate* danger of acquiring the disease, *e.g.*, those who have been exposed to a known case. It will provide them with an immediate immunity and permit them to deal successfully with any organisms or their products acquired as the result of the exposure. On the other hand, active immunisation should be used when there is no immediate risk, and thus the delay of a few days or weeks for the induction of immunity is not important. In practice this means that *active* immunisation should be carried out against the common infectious diseases unless the patient has been recently exposed.

The Mechanism of Resistance.—The protective mechanism

is very complicated and many tissues and body fluids take part in resisting infection: the lining membranes, tissue cells, particularly the white cells of the blood and the cells of the

TABLE II

EXAMPLES OF IMMUNE SERA

	Type of Serum	Source of Serum	Antigen used for actively immunising the Source
ANTITOXIC	DIPHTHERIA ANTITOXIN	HORSE (OR GOAT)	DIPHTHERIA TOXOID.
	TETANUS ANTITOXIN	HORSE	TETANUS TOXOID.
	DYSENTERY ANTITOXIN	,,	DYSENTERY TOXOID (SHIGA).
	SCARLATINAL ANTITOXIN	,,	SCARLATINAL TOXIN.
ANTIBACTERIAL	ANTIMENINGOCOCCAL SERUM	HORSE	MENINGOCOCCI.
	ANTITYPHOID SERUM	,,	TYPHOID BACILLI.
	ANTIPNEUMOCOCCAL SERUM	HORSE (OR RABBIT)	PNEUMOCOCCI.
ANTIVIRAL	CONVALESCENT MEASLES SERUM	HUMAN BEING	(RECOVERED FROM MEASLES).
	CONVALESCENT POLIOMYELITIS SERUM	,, ,,	(RECOVERED FROM POLIOMYELITIS).
	PLACENTAL EXTRACT	HUMAN PLACENTA.	

N.B.—When the antigen used is toxin or its derivative, toxoid, the serum is *antitoxic* and is called (*Disease*) *Antitoxin*.

When the antigen used is the organism itself, the serum is *antibacterial* and is called *Anti-(disease) Serum*.

Polyvalent sera are prepared by using as the antigen several strains or types of the same organism.

Monovalent sera are prepared by using one type only.

reticulo-endothelial system, the body fluids, vessels and nerves.

The lining membranes, such as the skin and mucosa, provide not only a mechanical barrier but exert some bacteriocidal action through their secretions. Saliva and gastric juice are examples of secretions possessing such properties.

The *reticulo-endothelial* system, which embraces widespread and differing types of cells, plays an important part in defence, and is probably responsible, among other things, for the production of antibodies. Organs which produce the white cells of the blood, particularly neutrophil leucocytes and lymphocytes, increase in activity when infection occurs. Usually their cells are produced in greater numbers and are carried by the blood from the place of production or storage to the site of infection. In consequence the number of such cells circulating in the blood increases. This leucocytosis is sometimes of value in diagnosis (see Blood, p. 67).

The masses of *lymphoid tissue* scattered throughout the body constantly guard the common portals of entry against invasion.

The *body fluids* are intimately concerned with resistance. Most is known of the *blood serum* with its important content of *antibodies*. Some antibodies have the power of attacking almost all organisms and are therefore *non-specific*, *e.g.*, *complement* and *opsonins*. Others, the *specific antibodies*, are capable of attacking only one organism or one type of organism. They do not appear until the specific infection occurs, *e.g.*, typhoid antibodies cannot be detected in the blood until some days after the onset of the disease. Once specific antibodies have been mobilised, they tend to persist and are thus ready to deal with any subsequent infection with the same organism. The specific antibodies are *precipitins*, *agglutinins*, *bacteriolysins*, *bacteriotropins* and *antitoxins*.

The Antigen-antibody Reaction.—The interaction of antibodies with antigens is one of the most important mechanisms in resistance. Bacteria are complex structures containing several antigens. The individual antigens, which are usually of a protein or complex carbohydrate nature, are sometimes confined to certain parts of the cell, such as the capsule or the flagellæ. Apart from the antigens in the cell itself, certain bacteria produce a *soluble exotoxin* in the fluid in which they are growing. Some antibodies combine with the antigen of the organism itself; some with the soluble antigens released when the bacterial cell disrupts; and others with the antigen of the exotoxin.

Precipitins cause the precipitation or flocculation of soluble endobacterial products, and thus the action takes place only in solution.

Agglutinins act on the organism itself, causing the bacteria to clump together or agglutinate, thereby interfering with their activity. Agglutination can be detected microscopically, or can be seen by the naked eye as a flocculation.

Bacteriolysins are concerned with the lysing or disruption of bacteria. The antibodies themselves are not destructive, but by attaching themselves to the bacteria they *sensitise* the organisms and render them susceptible to the action of the non-specific *complement* which completes the destruction.

Bacteriotropins are also sensitising antibodies. In this case the *coup de grâce* is given to the sensitised bacteria by another non-specific defender, the neutrophil leucocyte, which engulfs and destroys the organisms.

Opsonins have a similar action to bacteriotropins, but are non-specific, *i.e.*, they sensitise most organisms.

Antitoxins neutralise toxins. In vitro the toxin-antitoxin combination may result in specific precipitation or flocculation.

Under suitable conditions precipitation can occur in any of the antigen-antibody reactions. This is explained in the *unitarian* view of antibodies. It is suggested that there is only *one* specific antibody for each *pure* antigen, and that all antibodies are primarily sensitising. The union of a pure antigen with its specific antibody merely prepares the way for the final action of other substances in the blood. If the substance acting upon the antigen-antibody combination is an electrolyte, flocculation occurs; if it is complement, lysis results; and if leucocytes complete the work, phagocytosis occurs. Thus the different names—precipitins, agglutinins, lysins, etc.—are given to the *same* antibody, depending upon the end result of the process.

Practical Application of the Appearance of Antibodies.—The defence forces evoked by different infections vary, *e.g.*, agglutinins appear in the blood in enteric fever, and antitoxins in diphtheria and scarlet fever. Tests for the presence of these antibodies have been devised and are of value in clinical practice.

For example, to test for *agglutinins* the suspected serum is mixed with a suspension of a standard culture of the organism; a positive result is indicated by the appearance of flocculation. In clinical practice the presence of *antitoxins* in the blood above or below a particular level is indicated by the response to the intradermal injection of a small amount

of the appropriate toxin, *e.g.*, the Schick and Dick tests (*q.v.*). The examination of the blood for *bacteriolysins* involves the performance of complement-fixation tests, details of which should be sought in a standard work on Bacteriology.

Non-specific General and Local Resistance.—Apart from the specific resistance already described, there is evidence of the existence of a *general non-specific resistance* to bacteria. The factors responsible are uncertain, but leucocytes and substances contained in them probably play a part. This general bacteriocidal power of the blood can be increased by the injection of non-specific substances.

In addition, it is likely that a *local* immunity, also non-specific, exists, or can be set up. The resistance is confined to some single area of the body, *e.g.*, part of the skin or the nasal mucosa.

The importance of these non-specific factors is unknown, but it is probably not insignificant.

Effect of Diet, Vitamins, Fatigue and Atmospheric Conditions on Resistance.—The resistance of the body may be influenced by any of these factors. Rickets is a deficiency disease, the subjects of which are very liable to catarrhal infections.

Gross deficiency of vitamin A—the anti-infective vitamin—in a growing child is apparently associated with increased susceptibility to certain infections. Recently it has been shown that there is a disturbance of the metabolism of vitamin C (ascorbic acid) in certain infectious diseases, *e.g.*, in diphtheria there is poor elimination in the urine. Diet, too, apart from its vitamin content, appears to have some influence. It is well known that fatigue lowers general resistance, and rest is an important therapeutic agent. Fluctuations in the temperature and humidity of the air and the existence of fog lower the resistance of the respiratory tract. How these factors work is at present uncertain.

SUMMARY OF CHAPTER II

Results of Infection in a Susceptible Subject :

(*a*) Latent infection—no clinical signs.

(*b*) Overt infection—

(i) Disease, recovery and immunity.

(ii) Disease and death.

Results of Infection in an Immune Subject : No clinical signs ; organisms destroyed or become commensals (carrier state).

Factors Influencing Intensity of Infection : Depend upon species, virulence and velocity of infection.

Factors Influencing Resistance (Types of Immunity) :

1. Innate immunity.
2. Infantile immunity.
3. Acquired immunity.
4. Primary and secondary stimuli.
5. Artificial immunity—
    (*a*) Active : Injection of antigens.
    (*b*) Passive : Injection of antibodies (immune sera).
6. Non-specific resistance, local and general.
7. Diet, vitamins, atmospheric conditions, etc.

Types of Antibodies :

Specific—Precipitins, agglutinins, bacteriolysins, bacteriotropins, antitoxins.
Non-specific—Opsonins, complement.

CHAPTER III

HYPERSENSITIVENESS, ALLERGY, ANAPHYLAXIS AND SERUM REACTION

IN addition to producing disease and stimulating immunity, an infection may, after a latent period, induce a state of *hypersensitiveness* to the organism or its products. If so, re-exposure to the same infection results in a response of the tissues out of all proportion to the intensity of the infection, even sufficiently severe to produce illness. A number of disease processes have therefore been regarded as manifestations of hypersensitiveness. Some immunologists regard hypersensitiveness as a pathological process which is always harmful; others as a specialised response of the resistance-mechanism and therefore useful. It is to be regarded as an unusual manifestation of the reaction between antigen and antibody. The term *allergy* is often used instead of hypersensitiveness, but sometimes in a slightly different sense. *Anaphylaxis*, however, is a special variety of allergy and the term should not be used indiscriminately.

Not only micro-organisms but plants, pollens, chemicals, particularly proteins and complex carbohydrates, can set up a state of hypersensitiveness, of which there are several varieties :—

1. **Bacterial Hypersensitiveness** may follow an infection with almost any organism and is specific for that organism. It is rare in children but not uncommon in adults. It does not appear until several days or weeks after the onset of the infection, tends to persist for months or years, and is usually most marked after a recent infection. It can be detected by intradermal injection of dead bacteria or their products, hypersensitiveness being indicated by an indurated area of redness, which reaches its maximum in thirty-six to forty-eight hours and then fades. Rarely, general symptoms accompany the local reaction. The sensitivity to the proteins of the diphtheria bacillus, indicated by the pseudo-Schick and positive Moloney tests (*q.v.*) are good examples.

2. **Atopic Hypersensitiveness (Idiosyncrasies).**—Individuals with this type of hypersensitiveness react to exposure to the

antigen by developing attacks of such conditions as asthma, hay fever, eczema, drug and food idiosyncrasies. Skin tests are available, a positive reaction consisting in the appearance of an urticarial wheal in about ten minutes, reaching its maximum in about thirty minutes and fading in a few hours.

3. **Anaphylactic Hypersensitiveness or Anaphylaxis.**—This is typically an experimental state induced in animals. The response, when activated by the injection of the appropriate antigen, is a musculo-spasmodic one affecting smooth muscle in such structures as the bronchi, blood vessels and intestines. It differs characteristically in different animals.

A similar reaction occurs infrequently in man, but is not so typical. When it appears it does so after the injection of serum and is considered in detail in the next section.

4. **Serum Disease (Serum Sickness).**—Prophylactic or therapeutic injection of a foreign serum, usually horse serum, occasionally causes unpleasant reactions in hypersensitive individuals. The hypersensitive state may have been set up by the previous administration of serum, but reactions, occasionally severe, appear in individuals to whom the serum is given for the first time. The reactions are in no way related to the antibody content of the serum. The antibodies are mainly attached to the pseudo-globulins, and the reactions are due to other proteins in the serum, *e.g.*, albumens and euglobulins. *Concentrated* or *refined* sera are immune sera in which as much as possible of these harmful proteins has been removed. The pseudo-globulins with attached antibodies are separated by fractional precipitation and redissolved in saline. In some immune sera the antibodies are not distributed in this way, and refining results in considerable diminution in the efficiency of the sera. *Protein digested sera* (globulin-modified) are still further concentrated by enzyme action on proteins. This results in a smaller globulin-antitoxin molecule.

The *frequency* and *severity* of serum sickness depend upon—

(i) *The existence and the degree of hypersensitiveness of the subject.* The previous administration of serum increases any existing hypersensitiveness, or sets up a state of hypersensitiveness *after a latent period of about ten days.*

(ii) *The quantity of serum-protein injected.* This, in turn, depends upon the degree of refinement of the serum, and the quantity injected. Some therapeutic sera seem more liable than others to cause reactions.

(iii) *The route by which the serum is given.* Although reactions may follow the introduction of serum by any route, they are commoner after intravenous administration.

TYPES OF SERUM DISEASE

A. **Ordinary Serum Disease (" Serum Rash "—Serum Sickness).**—Although this type of reaction may occur after primary as well as subsequent injections, it is seen in its typical form in those receiving serum for the first time. It sometimes produces considerable discomfort, but is seldom serious and never fatal.

Following the administration of the serum there is a latent period of seven to fourteen days. With concentrated sera the manifestations which appear at the end of this time are usually *pyrexia* and an itching erythemato-urticarial *rash.* The pyrexia is seldom marked. The rash usually starts at the site of injection of the serum, and may be confined to this area. Usually, however, it becomes generalised, and patches of urticaria appear in other parts of the body within the next two days. The elements of the rash vary in size and form and may come and go quickly, so that its distribution and character may change considerably in a few hours. Occasionally the erythema is not urticarial, but scarlatiniform morbilliform, circinate, gyrate or a combination of these types. Ordinary serum sickness lasts from a few hours to two or three days—sometimes longer.

Formerly, with unrefined sera, more severe reactions were not infrequent ; they are rarely seen with modern concentrated and protein-digested sera. The chief manifestations, in addition to the rash and pyrexia, which are usually severe, are joint pains, albuminuria, œdema, *e.g.*, of the face, adenitis, malaise and vomiting. The adenitis, seldom marked, may be confined to the regional glands receiving the lymphatics from the site of injection, or may be generalised.

Changes are seen in the blood in serum disease : leucopenia, followed on recovery by eosinophilia, is the usual picture.

B. **Accelerated and Immediate Reactions to Serum.**—These unusual types are most likely to occur in those who have been previously injected. The most frequent effect of re-injection is to shorten the latent period between administration and the appearance of the reaction and to increase its intensity. If the effects of injecting serum appear within the first week (commonly two to four days) the reaction is described as

accelerated; if within an hour, as *immediate*. The immediate reactions are not infrequently associated with severe constitutional symptoms such as vomiting, rigor and collapse.

Sensitivity induced by the previous administration of serum does not ordinarily appear until about ten days afterwards, so that *re-injection can be carried out without fear during this period*. Thereafter sensitivity *may be* established, and the more closely the re-injection follows the primary one, the more likely is the reaction to be unusual, *e.g.*, re-injection three years after is less liable to cause trouble than one three weeks after.

Although the previous administration of serum, including that in prophylactics, may sensitise a patient in this way, in general it may be said that *there is little to fear from giving a second injection to any person who has not suffered severely from the first*. As a precaution, tests are carried out prior to re-injection to determine if sensitivity exists (*vide infra*).

C. **Anaphylaxis.**—An anaphylactoid reaction, which is the human counterpart of the anaphylaxis of animals, is dangerous but rare. It is confined to markedly sensitised patients, such as "horse asthmatics." Deaths have been recorded as occurring as quickly as a few minutes after the administration of minute quantities of horse serum (1 minim). The symptoms, which may come on during the injection, consist in collapse and cardiovascular, respiratory and alimentary disturbances. Pallor, restlessness, a poor thready pulse which becomes imperceptible, nausea, vomiting, diarrhœa, cough, wheezy and distressed breathing, cyanosis, prostration, sweating, coma and death may occur. The reaction is usually evoked in subjects who have *never had serum before*. Occasionally the practitioner may have some insight into the possibility of such a reaction, if the patient is known to be subject to other hypersensitive phenomena, such as asthma. The reaction is, however, specific, and only those asthmatics who are sensitive to horse products will respond.

D. **Other Rare Reactions.**

Local hypersensitiveness. Just as a local immunity may exist, so may a *local hypersensitiveness*, due to a *recent* previous injection of serum into that part of the skin. Re-injection may result in local pain, swelling, redness and even necrosis. This type of reaction (which corresponds with the *Arthus phenomenon* in animals) is extremely rare, but to avoid any possibility of it, re-injections should not be given into the same site as a recent previous injection.

Polyneuritis and paralysis due to serum have been described. The involvement may be localised, *e.g.*, to the brachial plexus, or more widespread.

Tests for Hypersensitiveness to Serum.—Tests are employed prior to the administration of immune sera, to determine if the subject is sensitive to horse serum. Unfortunately they are not reliable in the most serious type of hypersensitiveness—the anaphylactic—because there is no exact parallelism between dermal and general (constitutional) hypersensitiveness. In consequence, a patient with a negative test may still react severely to a subsequent injection of serum, and vice versa.

Of the tests employed, the most reliable is the *intradermal.* 0·2 c.c. of a 1 in 20 dilution of normal horse serum (or what is better, of the immune serum to be administered) is injected intradermally. A positive reaction—indicating hypersensitiveness—appears in ten to thirty minutes as an erythema, sometimes with an urticarial wheal in the centre.

The *ophthalmic test,* in which the diluted serum is dropped into the conjunctival sac, and the *percutaneous,* in which the serum is simply scratched into the skin, are unreliable.

Desensitisation (Hyposensitisation). — Desensitisation, or, more correctly, hyposensitisation, is a procedure for diminishing or eliminating hypersensitiveness. It has a wide application in the treatment of such conditions as asthma and hay-fever. The lowering of the hypersensitive state is rarely permanent; but if the patient's hypersensitiveness to horse serum can be temporarily diminished, therapeutic sera can be administered without serious effect. The principle consists in injecting very small graduated doses of the serum, in the hope that hypersensitiveness will be abolished. In rare instances of failure it may be necessary to replace immune horse serum by that of some other animal, *e.g.*, the goat.

Routes of Administration of Serum.—Therapeutic sera, to be effective, must be given by some route other than the alimentary canal. Administered by mouth or per rectum, the therapeutic effect is negligible. In the following table the parenteral routes used for the administration of serum are listed. For comparison, examples of the use of the routes for other purposes are also given.

Notes on the Routes

Percutaneous administration, performed by scratching the skin through a drop of serum, is unsatisfactory because the amount introduced is uncertain.

Intradermal administration is strictly intra-epidermal. The injection is made into the superficial layers of the epidermis.

It is usually painless and produces no bleeding, as it is superficial to the papillæ of the true skin. The amount

TABLE III

Route	Uses for Serum	Examples of Uses for other Substances
PERCUTANEOUS	(TESTS FOR SENSITIVITY)	VACCINATION AGAINST SMALLPOX. VON PIRQUET (TUBERCULIN) TEST.
INTRADERMAL .	(TESTS FOR SENSITIVITY) SCHULTZ - CHARLTON TEST	SCHICK, DICK AND MANTOUX TESTS.
SUBCUTANEOUS (HYPODERMIC)	(OLD ROUTE FOR THERAPY.) STILL USED OCCASIONALLY FOR DESENSITISATION, PASSIVE IMMUNISATION AND THERAPY	COMMON PARENTERAL ROUTE FOR MANY THERAPEUTIC SUBSTANCES. ACTIVE IMMUNISATION. SUBCUTANEOUS SALINES.
INTRAMUSCULAR	COMMON ROUTE FOR ALL THERAPEUTIC AND PROPHYLACTIC SERA	OCCASIONALLY USED FOR THERAPEUTIC SUBSTANCES, *e.g.*, BISMUTH, MERCURY, ETC.
INTRAVENOUS .	FOR RAPID ADMINISTRATION OF THERAPEUTIC SERA	OCCASIONALLY USED FOR THERAPEUTIC SUBSTANCES, *e.g.*, SALINES, GLUCOSE. INTRAVENOUS ANÆSTHETICS.
INTRA-PERITONEAL	OCCASIONALLY USED FOR THERAPEUTIC SERA	INTRAPERITONEAL SALINES.
INTRATHECAL .	FOR MENINGOCOCCAL SERUM	OCCASIONALLY USED FOR THERAPEUTIC SUBSTANCES. SPINAL ANÆSTHESIA.
INTRA-VENTRICULAR	FOR MENINGOCOCCAL SERUM	RADIOGRAPHY OF VENTRICLE.

injected is 0·2 c.c. (in America, 0·1 c.c.) and it produces a small, white, raised "button." Usually the flexor aspect of the forearm is used.

Subcutaneous or hypodermic administration. The injection is made into the connective tissue just under the skin. The abdomen, the outer aspect of the arm and the flexor aspect of the forearm are commonly chosen as sites.

Intramuscular administration. Any muscular part of the body may be selected. The outer side of the thigh (vastus externus) and the buttock are commonly used.

Intravenous administration. Usually one of the veins in the antecubital fossa (bend of the elbow) is chosen, commonly the median basilic. When in difficulty, any available vein will do, *e.g.*, the jugular, femoral, etc. For continuous intravenous therapy in children a vein on the inner side of the ankle is chosen. In infants with patent anterior fontanelles the injection can be made into the superior longitudinal sinus.

Intraperitoneal administration is carried out through the lower part of the anterior abdominal wall.

Intrathecal administration involves injecting the serum into the subarachnoid space, and necessitates performing lumbar or cisternal puncture.

Intraventricular administration. The serum is injected into a lateral ventricle of the cerebrum. In infants with patent anterior fontanelles, the lateral angle of the membrane is punctured. In older children and adults it is necessary to make a small hole in the skull.

Advantages and Disadvantages of Common Routes of Administration.—In most diseases for which immune sera are administered it is important that the serum reach the circulation quickly and be present in an effective concentration. Of the three routes commonly employed, the intravenous is the most rapid, the intramuscular is next, and the subcutaneous is the slowest. By the intravenous route all the serum enters the circulation at once and the maximum concentration is immediately attained. But there are drawbacks to its use. In infants, particularly those who are seriously ill, it may be difficult to enter the small collapsed veins; and at any age there is likelihood of unpleasant reactions—apart from the hypersensitive phenomena already described. Not infrequently a rigor and a variable degree of collapse follow within an hour. A similar response may appear after the administration of non-protein substances. Although in many respects this type

of reaction resembles "immediate" serum sickness, it appears to be distinct from the hypersensitive phenomena already considered. Ordinary serum sickness may follow after the usual latent period, suggesting that the two phenomena—the rigor and the serum disease—are distinct. The occurrence of rigors is lessened by warming the serum to body temperature and injecting it slowly. Because of these drawbacks the

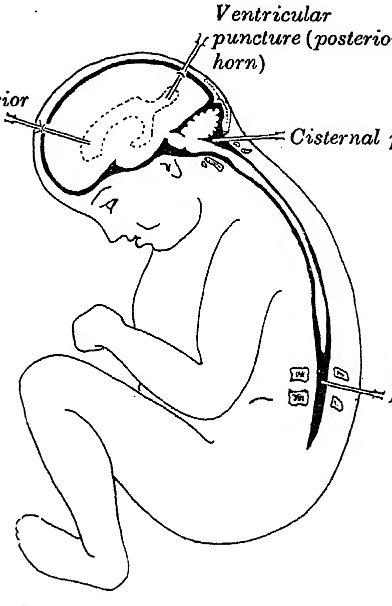


FIG. 2.—Puncture Sites for removal of Cerebrospinal Fluid.

intravenous route is reserved for cases in which delay of even a few hours is dangerous, *e.g.*, severe diphtheria.

By all routes other than the intravenous, the time of maximum concentration and the level of the serum in the blood are determined by the *rate of absorption* from the site of injection. From an intramuscular injection the maximum concentration is not reached until thirty-six to forty-eight hours afterwards, but there are no difficulties in administration and the dangers are few. With the subcutaneous route, absorption at the beginning—a most important time—is very much slower. There is, then, no justification for using the

subcutaneous route if the intramuscular is available, except in special circumstances, as in desensitisation, where slow absorption is desirable.

Intraperitoneal administration is sometimes employed when rapid absorption of serum is imperative and the intravenous route is impracticable.

Prevention and Treatment of Serum Reactions.—The following procedure should be adopted whenever serum is to be given :—

1. An inquiry should always be made for a history of—
   (*a*) asthma and allied conditions in the patient or family ;
   (*b*) previous administration of any type of serum ; the approximate date should be elicited.
2. As a routine a fresh solution of adrenalin 1 in 1,000 should be at hand.
3. Intravenous administration should not be attempted unless the patient is in bed, with facilities available for treating shock.
4. Serum should be warmed to body temperature and injected slowly. In selected cases in which the serum is being given intravenously, dilution of the serum with saline or glucose-saline helps to minimise reactions.

At the first signs of a reaction during the administration of serum, the injection should be stopped and 5 to 10 minims of adrenalin injected subcutaneously and repeated if necessary. If signs of collapse appear, the foot of the bed should be raised and hot-water bottles and blankets, or a shock cradle, applied. It may be necessary to administer oxygen and carry out artificial respiration. Other drugs which are sometimes used in this emergency are inhalations of amyl nitrite to combat the rise of blood pressure, and injections of atropine sulphate in large doses ($\frac{1}{100}$ to $\frac{1}{50}$ gr.) and pituitrin (1 c.c.) to relieve spasm of the smooth muscle. Morphia and atropine are also used for the reactions following intravenous administration.

As a prophylactic measure, adrenalin is sometimes given at the same time as the serum, particularly if the administration is intravenous. Adrenalin should *not* be given intravenously.

In ordinary serum sickness, although there is no danger, the prompt administration of adrenalin (5 to 10 minims) and ephedrine (gr. $\frac{1}{4}$ to $\frac{1}{2}$ three or four hourly, by mouth) may abort the attack. The adrenalin comes into action almost at

once, but its effect passes off quickly (usually in less than an hour); ephedrine takes longer to start, but its action is more lasting. In this way a continuous effect is produced. If treatment is delayed, even for half an hour, it becomes more difficult to influence the attack. For the rash, anti-pruritic lotions, such as spirit lotion and calamine lotion, provide some relief. Aspirin (gr. v to x four-hourly), sodium salicylate (gr. xv four-hourly), can be used for the joint pains, and liniment of methyl salicylate applied locally.

Special Precautions in Individuals Suspected to be Hypersensitive.—When it is suspected that the patient is hypersensitive, the following procedure should be followed :—

I. HISTORY OF PREVIOUS ADMINISTRATION OF SERUM.—Inject 0·2 c.c. of a 1 in 20 dilution of the therapeutic serum intradermally :—

(*a*) If no reaction results, follow up with the full therapeutic dose by the appropriate route in not less than half an hour.

(*b*) If a reaction occurs, repeat the dose of 0·2 c.c. of a 1 in 20 dilution intradermally at intervals of not less than half an hour until the reaction is minimal, then inject the remainder intramuscularly.

II. HISTORY OF ASTHMA OR ALLIED CONDITIONS OR OF REACTION TO PREVIOUS ADMINISTRATION OF SERUM.—Inject 0·2 c.c. of a 1 in 20 dilution of the therapeutic serum intradermally :—

(*a*) If within half an hour no reaction results, give 0·5 c.c. of undiluted serum intramuscularly. If this produces no reaction, give the full dose intramuscularly not less than half an hour later. The intravenous route in asthmatics is contraindicated.

(*b*) If a reaction occurs, fractionate the dose and administer the fractions subcutaneously at intervals of not less than half an hour. When the reaction becomes minimal, try a small fraction intramuscularly before administering the remainder by this route. In the highly sensitive, sera from animals other than the horse must be employed.

It may be necessary, or desirable, to vary this procedure according to circumstances, *e.g.*, the doses of the fractions can be varied ; or the interval of half an hour between injections can be increased if there is no urgency ; or the desensitisation may be

carried out intravenously (asthmatics always excepted), particularly if the therapeutic dose is to be administered by this route.

SUMMARY OF CHAPTER III

Types of Hypersensitiveness :

1. Bacterial. For detection : skin test. Result in twenty-four to forty-eight hours.
2. Atopic. For detection : skin test. Result in half an hour.
3. Anaphylactic. Tests for detection unsatisfactory.
4. Serum sensitiveness. Effect of injecting serum—
   (*a*) Ordinary serum sickness.
   (*b*) Accelerated reactions.
   (*c*) Immediate reactions.

   Tests for detection uncertain : intradermal test the best.

Prevention and Treatment of Serum Diseases :

1. Inquiry for history of hypersensitiveness or previous administration of sera.
2. Skin testing of subjects suspected to be hypersensitive.
3. Hyposensitisation (desensitisation) of susceptible subjects by fractional doses.
4. Injection of warmed serum slowly.
5. Administration of adrenalin, ephedrine, pituitrin, etc.
6. Use of sera other than horse serum.

Common Routes of Administration of Sera :

1. Intramuscular—for all ordinary purposes.
2. Intravenous, where speed is essential. Unpleasant reactions, *e.g.*, rigor and collapse, more likely than with 1.

CHAPTER IV

THE TRANSMISSION OF INFECTIOUS DISEASES

SOURCES AND MODES OF INFECTION

IN reviewing the ways in which infectious diseases are transmitted from one person to another, it is necessary to consider (i) the source of the infection, (ii) the manner in which the organism leaves the body of the first host, (iii) the method of conveyance to the new host, and (iv) the route by which the invasion of the new host is effected.

(i) **Sources of Infection.**—The primary source of an infection is almost always a human being, either suffering from the disease or carrying the organism ; he is the "infecting case" ; rarely an infected animal is responsible. It is sometimes impossible to detect the primary source, although some intermediate source may be readily discoverable. For example, the immediate source of an outbreak of enteric fever may be discovered to be infected oysters ; but the human being primarily responsible for the infection of the oysters may never be detected.

(ii) **Routes of Excretion.**—Organisms leave the body of an infected person in the *discharges* or *excreta*. Which discharges or excreta contain the organism depends upon the site of the disease. In diphtheria the nasal discharges are frequently infectious ; in enteric fever the fæces and occasionally the urine contain the organism. One type of discharge is of particular importance in the dissemination of the common infectious diseases. During coughing, sneezing, laughing and even talking everyone expels from the nasopharynx, nose and mouth fine **droplets** of mucus. Most of them are invisible, but a small proportion are large enough to be seen by the naked eye. If the upper respiratory tract is infected, as it is in many of the common infectious diseases, each droplet carries a number of organisms and is therefore infectious.

(iii) **Modes of Conveyance.**—Infectious discharges, droplets or excretions may be conveyed *directly* from one person to another, or they may contaminate some intermediate object or person, and reach their new host *indirectly*. The most

direct method is by actual contact between two individuals, as in kissing, or direct contact with discharges. This is relatively infrequent. By far the commonest direct method of conveyance is by means of droplets which are expelled from the first host and enter the second. The effective range of droplets is relatively small. Most of the droplets fall to the ground or on to objects in the vicinity. Some of the droplets are so small, or become so small by evaporation, that they remain suspended in the air. Convection currents and draughts may carry the falling or suspended droplets still greater distances, but this usually results in dilution of the droplet-laden air and consequent diminution of the mass of infection. In consequence, the distance across which an infection can be transmitted by droplets is seldom more than six to twelve feet. As most of the common infectious diseases are contracted as the result of direct transmission of droplets, it follows that the new host must be in relatively close proximity to the former one.

This has a direct bearing on the *aerial transmission* of disease. Formerly it was believed that some diseases, such as smallpox and chickenpox, could be conveyed through the air for long distances. This is not now generally accepted.

Apart from droplets, air may be infected by *dust*. Discharges or droplets fall to the ground and there dry up, constituting part of the dust. This dust may be disturbed by the activity of human beings or be carried for some distance by wind. But in the process of drying many organisms die, particularly if exposed to sunlight, which has a bacteriocidal action. Moreover, in the open air, and especially with a wind, the organisms are rapidly dispersed; and the further from the source of infection, the greater the dilution and destruction. This combination of drying, dilution and sunlight renders the concentration negligible and the air innocuous.

Knowledge of these facts explains many empirical beliefs concerning the spread of infectious diseases: the danger to others of coughing and sneezing without guarding the mouth and nose; the danger of acquiring infectious diseases in overcrowded places such as trams, buses, trains, theatres, cinemas, etc.; and the importance of proper ventilation, fresh air and sunlight in the avoidance of infection.

In the indirect methods of transmission, the discharges or excreta contaminate inanimate objects such as bed linen, handkerchiefs, clothes, books, toys, pencils and pens (*e.g.*, by sucking them), food and drink; or the hands, hair and clothes of an attendant. From these the infection is conveyed to the new host. The importance of inanimate objects (fomites) as

conveyors of infection has been exaggerated in the past. Organisms deposited on them dry fairly rapidly, particularly if exposed to the sun and air. Attendants, particularly in hospitals and institutions, are liable to play an important part in the transmission of disease. Sometimes the organism merely contaminates the hands or clothes; occasionally the infection is carried by the attendants in the upper respiratory tract. They are then temporary carriers. Insects, such as flies, and rodents, such as mice, act at times as intermediaries. In the case of flies, the insect acts merely as a conveyor; but rodents are usually themselves infected with the organisms they transmit.

(iv) **Routes by which Infection Enters**—*Portals of Entry.*—There are three common routes by which infection of the new host is effected: by *inhalation*, by *ingestion* and by *inoculation.* With some infections, such as with meningococci, typhoid bacilli, etc., the disease will not follow unless the organisms enter through the correct route; with others, such as with diphtheria bacilli, the organism enters most easily, but not invariably, through a particular channel. This preference of organisms for a particular route permits the classification of infectious diseases according to their mode of entry into the body. In Table IV organisms which can enter through various portals are listed more than once. Those diseases not considered in this book are printed in italics.

In the **inhalation** diseases the infection enters through the respiratory tract, usually as the result of inspiring air laden with infectious droplets. To this group belong the vast majority of the common infectious diseases: diphtheria, scarlet fever, measles, whooping-cough, chickenpox, cerebrospinal meningitis, acute poliomyelitis, etc.

In infection by **ingestion** the organisms enter through the alimentary canal, usually as the result of the consumption of infected food or drink. The conveyance is therefore indirect and the first host may be near or at a considerable distance from the new one. Excreta are the common sources of infection of the ingestion diseases, of which examples are the enteric fevers, the dysenteries and infectious enteritis of children. Modern methods of sanitation ensure that excreta are properly disposed of and are not allowed to contaminate water and food supplies. Moreover, such hygienic measures as the efficient filtration of water, the pasteurisation of milk, the minimum handling of food and the personal cleanliness of those who have to prepare food have all combined to minimise transmission by this route. In consequence the

TABLE IV—TYPES OF ÆTIOLOGICAL AGENTS AND MODES BY WHICH THEY PRODUCE INFECTION

(*a*), (*b*) and (*c*) indicate the order of frequency of the mode of infection. Diseases in italics are not described in this book

TYPE OF ÆTIOLOGICAL AGENT.	MODES OF INFECTION				
	INHALATION	INGESTION	INOCULATION: Direct	INOCULATION: Indirect, *i.e.*, vector necessary	UNKNOWN OR UNCERTAIN
BACTERIAL: (i) Essentially local infections.	Diphtheria. Scarlet fever (*a*). Infectious sore throat. Pertussis. *Tuberculosis* (*a*).	Bacillary dysenteries. Scarlet fever (*c*). *Tuberculosis* (*b*).	Tetanus. *Anthrax.* Surgical and puerperal scarlet fever (*b*). Erysipelas. *Impetigo.* *Gonorrhœa.* *Tuberculosis* (*c*).	*Plague* (*rat flea*) (*a*).	*Actinomycosis.* *Leprosy.* Tularæmia.
(ii) Essentially bacteriæmias.	*Acute pneumonia* (*lobar*). Cerebrospinal fever.	Enteric fevers. Brucellosis.	Puerperal septicæmia.	*Plague* (*rat flea*) (*a*).	
VIRAL.	Measles. Rubella. Smallpox. Chickenpox. Mumps. Acute poliomyelitis. Epidemic encephalitis. *Common cold.* Influenza.	...	Vaccinia. *Lympho granuloma venereum.*	Typhus (louse). *Dengue* (*mosquito*). *Yellow fever* (*mosquito*). Trench fever (louse). *Rabies* (*dog*). *Rat-bite fever* (*rats*). Relapsing fever (louse).	Psittacosis (Parrot). Benign lymphocytic meningitis. Herpes zoster. Herpes febrilis. Epidemic catarrhal jaundice.
VIBRIAL.	...	*Cholera.*	...	...	...
SPIROCHÆTAL.	...	Weil's disease (*b*).	*Syphilis.* Weil's disease (*a*).	...	Fuso-spirillosis (Vincent's).
PARASITIC.	...	Amœbiasis.	*Schistosomiasis.*	*Malaria* (*mosquito*). *Sleeping sickness* (*tick*).	...
FUNGAL.	...	...	*Favus.* *Ringworm.*	...	...
UNKNOWN.	...	Infectious enteritis.	...	...	Infectious mononucleosis (Glandular fever). *Acute rheumatism.*

ingestion diseases are much less frequent than they were, and when outbreaks occur are readily controlled. Cases which appear are usually attributable to the unclean handling of food by infected persons, such as carriers.

The **inoculation** diseases are contracted as the result of an infection of the skin or mucous membrane. To permit the organisms to enter, some breach of the surface is necessary, although this need be only such microscopic damage as exists in almost everyone. The mode of conveyance may be direct, as by contact with infectious discharges; indirect, by contaminated hands, instruments, etc.; or by droplets coughed or sneezed on to the cutaneous lesion. Auto-infection occasionally occurs, *e.g.*, hæmolytic streptococci carried in the throat and causing no damage there may, if conveyed to some other part, such as the skin, set up a disease process in their new habitat.

A special variety of inoculation diseases necessitates the intervention of an *insect vector.* Such diseases are rare in this country. With some infections the organism passes part of its life-cycle in the vector before being able to infect man, as in malaria; with others the infection in the vector and the human being is with the unchanged organism.

This classification of infectious diseases according to the mode of transmission and portal of entry is not rigid. Although the inhalation diseases are conveyed from one respiratory tract to another by droplets, and the ingestion diseases from one alimentary canal to another by food or drink, exceptions are not infrequent. For example, although the hæmolytic streptococci causing scarlet fever are usually conveyed from *throat* to *throat* by droplets, occasionally the droplets from the first host infect the perineum in a puerperal woman. Scarlet fever can also be contracted by the ingestion of infected milk, or may be conveyed indirectly by attendants. Again, tubercle bacilli may enter the body through the respiratory tract by the inhalation of droplet-infected air; or by the alimentary tract from the ingestion of infected milk; or they may be inoculated into the skin. The form of the disease is different in each case.

New hosts are therefore infected—

(*a*) By actually *touching* the primary case. The transmission is by *direct* contact with *discharges.* The old idea that touching a patient anywhere was sufficient is inaccurate. The part touched must be infectious and the part touching must be capable of being infected. Kissing is probably the most important example.

(*b*) By being in *close proximity* with the primary case. The transmission is usually *direct*—by *droplets* through the air. It is the commonest method and the only type of aerial transmission which is important.

(*c*) At a *considerable distance* from the first primary case—by *indirect* transmission.

Relationship of the Portal of Entry to the Locus of the Disease.—Usually the site of entry of the organisms is the main location of the disease, *e.g.*, most inhalation diseases produce manifestations in the upper respiratory tract as an essential clinical feature. Occasionally this is not so: the local lesion may be absent or insignificant, the main manifestation of the disease being in some distant organ, *e.g.*, in acute poliomyelitis and in cerebrospinal meningitis the organism enters through the nose or nasopharynx, but the striking clinical feature is the involvement of the central nervous system. These things depend largely upon what happens to the organism after it enters the body. With some infections the disease is essentially a local one. The growing organisms are restricted to a local site and elaborate toxins which circulate and produce the general effects. Examples are erysipelas, scarlet fever, diphtheria and simple sepsis. With other diseases the organism invades the blood stream, producing a bacteriæmia, which usually localises itself in some tissue for which the organism has a particular affinity. Cerebrospinal meningitis is an example: the meningococcus enters through the nasopharynx, invades the blood stream and settles in the meninges where it sets up an inflammation.

Duration and Intensity of Infectivity.—In the past, patients with infectious diseases were isolated until they were well, because it was thought that the period of infectivity to others corresponded with the period of illness. Whilst it is still the practice to isolate patients during their illness, it is now known that many are free from infection whilst still ill, and others may remain infectious after they have recovered. In almost all diseases the patients are most highly infectious in the very early stages of their illness; thereafter infectivity declines with varying rapidity, depending upon the infection and the individual. In chickenpox and rubella infectivity passes off rapidly—in a few days at most. In diphtheria and whooping-cough the majority are free from infection in three or four weeks, although some may clear much earlier, and others persist much longer. In the occasional *convalescent carrier* infectivity persists for a variable time after the patient has recovered. Lastly, it is probable that in some diseases the

patient is infectious for a short time before the first clinical signs appear, *i.e.*, towards the end of the incubation period.

This knowledge has profoundly influenced the outlook on epidemics and their prevention by isolation. Since many patients are most highly infectious before they receive medical attention or can be diagnosed, isolation cannot prevent the spread of infectious diseases to any considerable extent.

Release Cultures.—In diseases in which the causative organism is known and can be readily isolated, this decline in infectivity in the course of the illness can be determined by periodic bacteriological examinations. In diphtheria this is the practice. Patients are not considered free from infection, and therefore not fit to be discharged, until they have had two consecutive negative bacteriological examinations of swabbings. These *release cultures* are also employed in enteric fever, dysentery and cerebrospinal meningitis. In scarlet fever difficulty arises because of the ubiquitousness and multiplicity of types of hæmolytic streptococci. In the present state of our knowledge it is difficult to assess the importance of a positive culture taken before discharge ; in whooping-cough the method is at present generally inapplicable because of the technical difficulties of isolating the organism. In some diseases, therefore, discharge from isolation depends entirely on clinical evidence ; in others, upon the additional information obtained from release cultures.

SUMMARY OF CHAPTER IV

Primary Source : An infected person suffering or carrying.

Mode of Exit from the First Host : In discharges, droplets and excreta.

Mode of Conveyance :

(*a*) *Directly*, from person to person (close proximity).
(*b*) *Indirectly*, through some intermediary or inanimate object.

Mode of Entry into New Host : By inhalation, ingestion or inoculation.

Types of Disease :

(*a*) Essentially local.
(*b*) Essentially a bacteriæmia.

Infectivity : Greatest at the beginning of the illness ; declines fairly rapidly. Utility of release cultures.

CHAPTER V

DIAGNOSIS

I. GENERAL CLINICAL MANIFESTATIONS

WHENEVER there is doubt, or as confirmation of a clinical diagnosis, laboratory tests to assist the clinician are, in many instances, available, but a disease must not be diagnosed on laboratory reports alone; the final decision must depend upon clinical evidence.

Clinical Course of Infectious Diseases.—The course of an infectious disease is marked by clearly defined stages. The *infection*, which usually produces no disturbance of the patient, is followed by a quiet or latent period, the *incubation period*, during which signs of ill-health are usually absent. At the end of this time the *invasive stage* occurs, proclaiming the *onset of the disease* with its prodromal manifestations. The symptom-complex thus initiated evolves during the *fastigium* or *period of advance*, until the height or *acme* in the disease is attained. The fastigium may last for a variable time, from a few hours to days or weeks, and may terminate in *recovery* or *death*. Recovery is heralded by the onset of a stage of *decline* or *defervescence*, which may be gradual or sudden and is completed by a period of *convalescence*, during which the general strength returns to normal. In some instances the disease fails to develop fully: it *aborts* at some stage short of the acme.

The stage of advance or the period of convalescence may be interrupted by the appearance of *complications*, extensions of the disease beyond its usual bounds, which may themselves prove fatal. *Remissions*, temporary abatements of symptoms, are sometimes seen during the clinical course of the disease. The stage of decline may be interrupted by a *recrudescence*, and the stage of convalescence by a *relapse*, in both of which symptoms return. In relapses the syndrome of the initial illness is repeated, usually in a milder form. Occasionally the relapse proves fatal.

Incubation Period

The incubation period is the time which elapses between the entry of the organism and the onset of the disease. It is

usually a quiet period, but sometimes vague symptoms are experienced by the patient. Except that the organisms are multiplying, the changes in the body and the parasite-host relationship are unknown. The hypothesis that incubation is a latent period analogous to that occurring in allergic reactions, and that the disease itself is an allergic manifestation, is not proved.

Although all infectious diseases have incubation periods, the duration varies in the different diseases. Within certain limits there are variations in the same disease. Usually for each disease the common limits and the extreme limits are given separately. The student is advised to familiarise himself with the general classification given below before learning the more exact periods which are given under the separate diseases.

1. **Short.**—The disease appears in the *first week* after exposure, *i.e.*, *within seven days.*

Diphtheria.	Cerebrospinal fever.
Scarlet fever.	Erysipelas.
Influenza.	Septicæmia.

2. **Medium.**—The disease appears in the *second week* after exposure, *i.e.*, *from seven to fourteen days.*

Measles.	Smallpox.
Whooping-cough.	Enteric fever.

3. **Long.**—The disease appears in the *third week* after exposure, *i.e.*, *from fourteen to twenty-one days.*

Mumps.
Chickenpox.
Rubella.

Exceptionally short or long incubation periods are probably more apparent than real. They suggest that the time of infection has been miscalculated, *e.g.*, by missing an intermediate case. Inaccuracy may also depend upon the difficulty of deciding when symptoms commenced.

The Disease

(*a*) PRODROMAL SYMPTOMS.—The onset of the disease proper may be sudden, as in scarlet fever, or gradual, as in enteric fever. In most infectious diseases the illness is ushered in by the appearance of constitutional or *systemic* symptoms. These symptoms, called *prodromal* because they appear early, before the characteristic features of the disease, are not peculiar to any one disease. Although one or more of them tend to be

emphasised at the beginning of certain infections, they are merely indicative of *an* illness rather than a *specific* illness. It may therefore be impossible in the early stages, before the characteristic signs appear, to make a definite diagnosis, although it is obvious that the child is "sickening for something." Pyrexia, headache, malaise, restlessness, prostration, pains in the limbs and back, nausea, vomiting, a chilly feeling, shivering, a rigor, or, in children, a convulsion are common but not inevitable at the onset of several of the specific fevers. Their occurrence imposes two primary steps upon the practitioner which must never be omitted in *any* sick child : to take the temperature and examine the throat.

(*b*) SPECIFIC SYMPTOMS.—The specific or characteristic symptoms may be local and systemic, or systemic only.

Local symptoms may be

(i) referable to the portal of entry ;
(ii) indicative of the localisation of the disease elsewhere.

Since infection by inhalation is common, symptoms referable to the respiratory tract are frequent—so much so, indeed, that they almost lose their specificity. The commonest are sore throat, coryza (running nose and eyes) and cough. Many diseases begin with one or more of these ; but sore throat is particularly a feature of such diseases as scarlet fever and diphtheria ; coryza appears in the common cold, measles and rubella ; and cough in whooping-cough and measles. Certain common groupings of prodromal and local symptoms occur, of which headache, vomiting and sore throat are an example. In some diseases the local manifestations at the site of entry are characteristic, *e.g.*, the appearance of the throat in diphtheria. In others they may be quite inappreciable, but are followed by manifestations in some other part of the body, indicating the localisation of the disease there, *e.g.*, in cerebrospinal fever and acute poliomyelitis upper respiratory symptoms are common but subordinate to the most characteristic signs which appear in the central nervous system.

General or Systemic Symptoms.—Of the constitutional symptoms which appear in infectious diseases, all are due to general effects of the organism or its toxic products. Some have been described under prodromata ; others are so characteristic as to be classed as specific. Of the latter, one of the most striking is the appearance of a rash (see p. 57). The same symptom may be prodromal or specific, *e.g.*, a rigor is commonly a prodromal symptom, but rigors are a characteristic feature of septicæmia and malaria.

In some diseases constitutional symptoms are trivial or absent and the diagnosis may depend upon the appearance of one pathognomonic feature only, *e.g.*, in chickenpox and rubella the typical rash may suddenly appear in an otherwise healthy person.

In those diseases where the organisms grow locally and their soluble products—toxins—circulate in the blood stream, the generalised condition is a *toxæmia, e.g.*, erysipelas, scarlet fever and diphtheria. If the organisms themselves are carried in the blood stream to their ultimate location, the condition is a *bacteriæmia, e.g.*, cerebrospinal fever. In such cases the presence of the organism in the blood stream is usually transitory. When, however, the organisms persist in the blood, and even multiply there, a *septicæmia* is set up, *e.g.*, puerperal septicæmia. If these circulating organisms settle in different organs and produce abscesses the condition is a *pyæmia.*

Toxæmia and the Typhoid State.—Toxæmias of whatever bacterial origin have many manifestations in common; but some toxins have a special and peculiar action because they have a selective affinity for certain tissues, *e.g.*, the toxin of tetanus for motor neurones, that of diphtheria for heart muscle and nerves, and that of scarlet fever for the skin. Despite this, all circulating toxins, whether exotoxins or endotoxins, affect all tissues to a varying degree, causing constitutional changes varying from a mild indisposition to a grave disturbance of the general health which may result in death. Some of the symptoms have already been mentioned under prodromata: pyrexia, headache, malaise, restlessness, anorexia, nausea, vomiting, pains in the limbs, etc. The severer toxic states usually appear later, as the result of the more prolonged action of the toxin. Because it is not uncommon in *typhoid fever*, the syndrome associated with a severe toxæmia has been called the *typhoid state,* although the same manifestations may appear in any severely toxic case of an infectious disease.

In the *typhoid state* there is evidence of involvement of all organs. For simplicity the manifestations may be classified as physical and nervous. There is marked muscular weakness, which advances to prostration, the patient tending to slip to the foot of the bed. The heart is dilated, the sounds are of poor quality, the pulse is rapid and soft, and the blood pressure low. The colour is poor, usually pale with a cyanotic tinge. The tongue is dry, brown and furred. Sordes collect around the lips and teeth. The eyes are dull and the pupils dilated. The lungs are congested. Albuminuria is present and the urine is scanty and concentrated. Diarrhœa is common.

Incontinence of urine and fæces may occur. The sensorium is clouded, the patient passing from a state of simple drowsiness to semi-consciousness and then coma. The dull, half-open eyes of the semi-conscious patient unaware of his surroundings have suggested the term "coma vigil" for this appearance. Delirium of the low type, in which the patient mutters incoherently, appears. Involuntary muscular twitchings and movements are common; the hands are tremulous, twitchings of the limbs occur (*subsultus tendinens*) and the patient picks at the bed clothes (*carphologia*). The tremulous tongue is protruded with difficulty if the patient is sufficiently conscious to understand the request. The physical and mental prostration may advance to death, or the condition may gradually mend. The best criteria of the severity of the toxæmia, and therefore the most useful prognostic signs, are the gravity of the effects upon the heart and nervous system.

Bacteriæmia.—The spread of organisms is not an uncommon feature in infectious diseases, *e.g.*, enteric fever, cerebrospinal fever, lobar pneumonia, brucellosis.

It is a stage in the ordinary evolution of the disease—a preliminary to the appearance of the characteristic signs in the specific location. In all these, however, the organism is present for a short time and in relatively few numbers, usually at the beginning of the disease. In consequence it is often difficult to isolate the organism from the blood stream. Occasionally this bacteriæmic phase may be sufficiently severe to be called a septicæmia, and death may occur before the typical local signs appear, *e.g.*, in severe cases of cerebrospinal fever.

Septicæmia.—In septicæmia the organisms in the blood stream persist, either because the supply is being maintained or because they are not being eliminated. There is, of course, no fundamental difference between bacteriæmia and septicæmia, but it is convenient to be able to differentiate the transient and "normal" state from the persistent or abnormal one, *e.g.*, the appearance of hæmolytic streptococci in the blood stream in scarlet fever, typically a local disease, is best described as a septicæmia.

Pyrexia.—The increase in the temperature of the body which commonly occurs in infectious diseases is referred to as "pyrexia" or "fever." "Pyrexia" is the better term because it refers to one sign only—elevation of temperature. "Fever" is less satisfactory because it is used not only for the *sign* "pyrexia" but also for the *symptom-complex* which almost invariably accompanies pyrexia. "Fever" is also used as a

synonym for "infectious disease"—even although some diseases do not cause a rise of temperature.

Pyrexia, and the constitutional symptoms which accompany it, are evidence of the increased metabolic activity of the body due to the action of the toxin. Since a rise in temperature is in the nature of a defence reaction, attempts should not be made to diminish it by the use of depressing drugs. The rational method of reducing temperature is to treat the condition giving rise to it. Occasionally pyrexia, particularly if excessive (hyperpyrexia), may of itself produce harmful effects, and measures to lower the temperature may be necessary. Although antipyretic drugs such as aspirin, phenacetin and phenazone are exhibited, it is better to use physical agents such as tepid sponging or baths.

The constitutional symptoms accompanying pyrexia may include any of the following: a chilly feeling or rigor, often indicating the onset, malaise, headache, nausea, vomiting, diminution in the bodily secretions, *e.g.*, dry skin, scanty albuminous urine, constipation, restlessness, weakness or prostration and quickening of the pulse. These are similar to the prodromata which have already been described as due to toxæmia, and in a particular case it may be difficult to decide which are due to the toxæmia and which to the pyrexia. Although the association of pyrexia and constitutional symptoms is usual, sometimes severe toxæmias occur without pyrexia, *e.g.*, toxic diphtheria; on the other hand, pyrexia, particularly in children, may occur without constitutional symptoms of any sort.

Temperatures may be taken by mouth, per rectum, or in a flexure of the skin, such as the axilla or groin. Rectal temperatures, which are the most accurate, may be as much as 1° above the mouth reading. Skin temperatures are least satisfactory: they are usually lower than mouth temperatures. In the infectious diseases limitations are imposed upon the method of taking the temperature because most patients are children, and because of the presence of infection. The axilla or groin are the sites usually employed, despite their occasional untrustworthiness.

Two features of the normal temperature chart are important, as variations in one or both of them may occur, viz. :—

(i) The *height* of the temperature, which is normally about 98° F. when taken by mouth.

(ii) The *diurnal range*; a variation of from 0·6° to 1° F. between the morning and evening temperatures occurs, the maximum being reached at about 6 P.M. and the minimum in the early morning.

In infectious diseases the type of pyrexia is often of considerable assistance to the clinician. The temperature curve, like the course of the disease, can be divided into the onset, the fastigium and the decline. At the onset the rise in temperature may be abrupt, as in lobar pneumonia, scarlet fever and typhus fever, or gradual, as in the staircase temperature of the first week of typhoid fever.

Once established, the pyrexia may be *regular* or *irregular*. Three types of the former are usually described. In *continued* pyrexia the temperature is above the normal for days, but there is little or no increase in the diurnal range. This occurs in lobar pneumonia, typhus fever, smallpox (certain stages) and often in the second week of typhoid fever. In *remittent* pyrexia not only is the temperature constantly above normal,

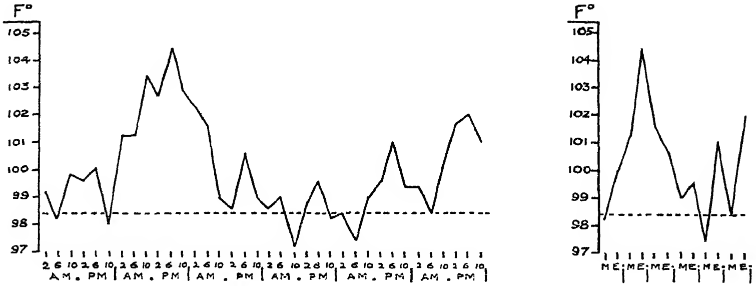


FIG. 3.—Comparison of (*a*) Four-hourly Temperature Chart, (*b*) Morning and with Evening Temperature Chart from the same Patient over the same Period of Time.

but the diurnal range is increased. This is seen in some cases of tuberculosis (hectic temperature), broncho-pneumonia, empyema, puerperal septicæmia, etc. In *intermittent* pyrexia the daily range is increased, and although the level is above normal for most of the day, it reaches the normal level at some time in the twenty-four hours. The best example of regular intermissions of temperature occurs in malaria. The irregular types of temperature may show combinations of these, *e.g.*, in pyæmia and certain septic conditions a continuous temperature may occur with irregular intermissions and remissions.

The fall in temperature back to normal may take place slowly—by *lysis*—as in typhoid fever and broncho-pneumonia, or abruptly—by *crisis*—as in typhus fever and lobar pneumonia. The terms "lysis" and particularly "crisis" are used to describe not only the fall in temperature, but also the improve-

ment in the patient's condition. In crisis there is a sudden improvement in all the symptoms, attributed to a sudden development of immunity. The lay use of the word " crisis " to indicate a time in the disease when the result is in the balance is scientifically inaccurate. *False crises* occur in which

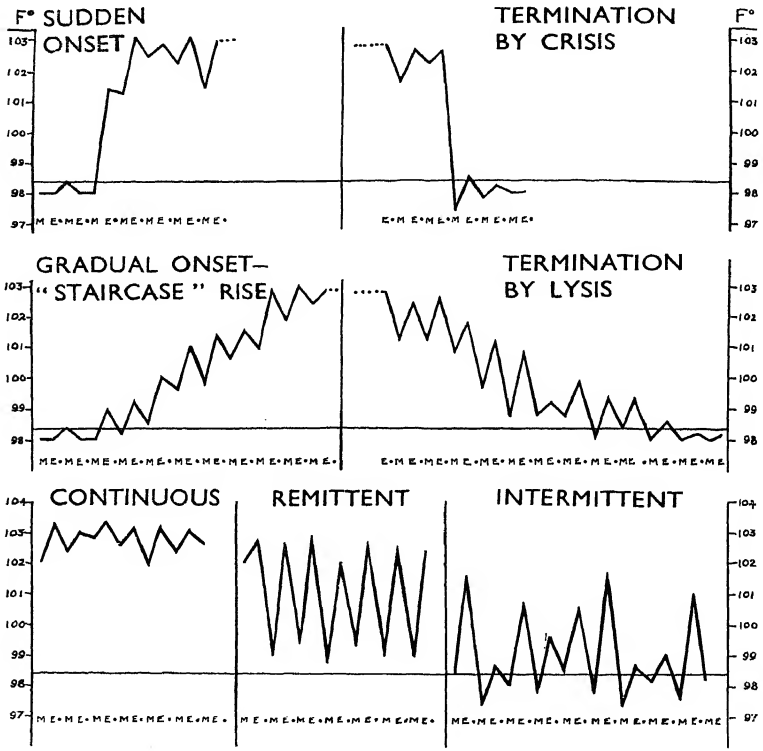


FIG. 4.—Types of Pyrexia.

there is a sudden fall of temperature without a corresponding improvement in the patient's condition, and often without a corresponding fall in the pulse rate. These false crises are more in the nature of a collapse and indicate a sudden turn for the worse.

In some infectious diseases pyrexia is an almost constant finding, *e.g.*, scarlet fever, measles, smallpox ; in others, *e.g.*,

rubella and chickenpox, it is usually trivial or absent. In many diseases pyrexia, when it occurs, pursues a typical course. In typhoid fever, for example, there is a gradual rise in the first week, followed by seven to ten days of continuous pyrexia, and a decline by lysis lasting a week or more. In lobar pneumonia the temperature rises abruptly in the first twenty-four hours, remains continuous for five to ten days, and terminates by crisis. In scarlet fever the temperature usually rises sharply, reaches a maximum in two to three days, and declines slowly during the next two or three days. Some diseases exhibit peculiarities of temperature at certain stages of the illness, *e.g.*, in smallpox there is often a transient drop in temperature with the onset of the rash, and a change in the type of temperature when the rash pustulates ; in measles there is often a temporary exacerbation of pyrexia with the onset of the rash.

Although the degree of pyrexia is usually an indication of the severity of the disease, it must be remembered that variations are common in both health and disease, and that the behaviour of young children is sometimes extremely perplexing. In healthy children the height of the temperature may be above or below the usual level ; trivial disorders may produce considerable elevations of temperature ; severe complications, such as mastoiditis, sometimes cause no pyrexia ; and occasionally in children *reversion* of the daily range occurs, the morning temperature being higher than the evening.

Varieties of an Infectious Disease.—Most patients with an infectious disease suffer a *simple, ordinary* or *typical* attack, *i.e.*, a number of common clinical manifestations appear and approximate in severity to an average for that disease. But in every infectious disease variations from this average occur. *Mild* types and *severe* types explain themselves. In *abortive* types the disease fails to develop fully ; the mode of onset suggests the beginning of the disease, but the characteristic signs either do not appear or are so slight and transient as to constitute a marked departure from the typical type. Abortive attacks are usually so mild and atypical as to be readily missed. This is less likely to occur during epidemics because closer watch is kept for cases of the disease. Another type occasionally seen is the case which fails to develop the characteristic rash. This may be due to the mildness of the attack, which may therefore be called abortive ; or it may depend upon the overwhelming severity of the attack, which so depresses the functional activity of the skin that it fails to respond with a

rash; or it may be due to the existence of a resistance or immunity in the skin not shared by the rest of the body.

In *modified* attacks the mildness of the disease is due to a partial protection conferred by previous immunisation, *e.g.*, children who have been *passively* immunised with convalescent measles serum shortly before contracting measles develop a mild, atypical attack; similarly, those who have been *actively* protected against smallpox by vaccination, and who contract the disease some years later when immunity is waning, develop a modified attack. *Toxic* types occur in some diseases, the striking feature being the severity of the general toxæmia, which overshadows the characteristic signs of the disease. In *septic* types the feature is a tendency to develop suppurative lesions. Very severe types, in which death occurs before the characteristic signs appear, are known as *fulminating* attacks. If hæmorrhages occur into the skin and mucous membranes, the type is described as *hæmorrhagic* (see p. 61). Fulminating and hæmorrhagic attacks, like abortive ones, are less likely to be missed during epidemics than at other times. *Second* attacks occasionally occur weeks, months or years after the initial attack, but most infectious diseases confer a lasting immunity.

SUMMARY OF CHAPTER V

Course of Infectious Diseases:

Infection, incubation period, onset, fastigium, acme, decline, convalescence.

Complications, recrudescences and relapses.

Symptoms:

1. Prodromal and specific; local and general.
2. Toxæmia and the typhoid state (muscular prostration, including cardiac weakness and nervous manifestations).
3. Bacteriæmia—sparse transient invasion of the blood stream by organisms.
4. Septicæmia—persistent invasion of the blood stream by organisms.
5. Pyrexia—
   - (i) Onset: (*a*) Abrupt; (*b*) Gradual.
   - (ii) Fastigium: (*a*) Regular—continuous, remittent, intermittent; (*b*) Irregular.
   - (iii) Termination: (*a*) Crisis; (*b*) Lysis.

Varieties of Infectious Disease: Simple (ordinary, typical), mild, severe, abortive, modified, toxic, septic, fulminating, hæmorrhagic. Second attacks.

CHAPTER VI

DIAGNOSIS (CONTINUED)

II. THE RESPIRATORY TRACT, THE FAUCES, AND THE MIDDLE-EAR CLEFT

AS many infectious diseases result from the inhalation of organisms, a local lesion of the respiratory tract or fauces is a common clinical feature; and sore throat, coryza and cough are common symptoms.

Sore Throat.—On examining the throat by depressing the base of the tongue, the structures which are revealed are those bounding the opening from the mouth to the oropharynx: the tonsils in their fossæ, bounded in front and behind by the anterior and posterior pillars of the fauces, and together forming the fauces; the margin of the soft palate and the uvula; and through the opening, a part of the pharynx. Sore throat is a symptom of inflammation, not only of the tonsils but of these neighbouring structures. In fact, most inflammatory changes in this situation tend to involve all the structures to a variable extent. Although a sore throat may occur in many infectious diseases, it is a particularly important symptom of scarlet fever and faucial diphtheria, because a local lesion in this situation is an essential clinical feature of these diseases. The pathological changes which can be seen are usually two: inflammation and the presence of a deposit. The type of change present is of considerable diagnostic importance.

In *scarlet fever* the appearances are those of an acute tonsillitis. (There is, in fact, no difference between the local lesion of scarlet fever and acute tonsillitis, because they are both due to the same organism acting in the same way.) The condition is really a tonsillo-pharyngitis, as all the structures of the throat are bright red and often swollen, although the swelling particularly affects the tonsils. There is often no deposit at all—*catarrhal tonsillitis*. When a deposit is present it most commonly takes the form of a number of separate white or yellow spots on the tonsils—*follicular tonsillitis*. Occasionally the deposit forms uniform white patches covering

the tonsils, but rarely extending beyond them. The deposit is soft, white, readily scraped off and no bleeding follows its removal. The tonsillar glands—the cervical glands which drain the tonsils—are usually slightly enlarged and tender.

In *diphtheria* faucial injection and swelling are rare except in severe cases. A deposit is, however, the rule. It takes the form of a patch or patches of adherent, smooth greyish-white membrane. If it is forcibly removed a little bleeding occurs from the surface of the mucosa, which, however, shows no gross destruction of its surface. The membrane may be limited to the tonsils or may extend or be restricted to one or more of the following neighbouring structures: the pillars of the fauces, the uvula, the palate and the pharynx. Indeed, the presence of a deposit beyond the tonsils should suggest diphtheria.

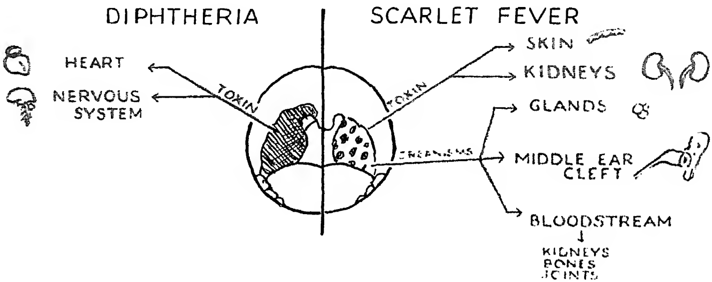


FIG. 5.—Mechanism of Diphtheria and Scarlet Fever compared.

Another condition in which a membrane may occur on the tonsils or neighbouring structures is *Vincent's angina*, but here the membrane covers the surface of an ulceration of the mucosa.

Angina connotes strictly a feeling of suffocation due to any cause, *e.g.*, faucial angina, angina pectoris. Not infrequently "angina," unspecified, is used when *faucial angina* is meant; and sometimes the word is used as a synonym for *sore throat* without any sensation of suffocation.

In both scarlet fever and diphtheria the local lesions are due to the multiplication of the causative organisms. Effects are, however, discernible elsewhere in the body, as in both diseases toxins are produced at the site of the local lesion and circulate in the blood stream. In addition to the general symptoms of toxæmia (see p. 38), others occur due to the affinity of the toxin for particular tissues; that of diphtheria

affects heart muscle and nervous tissues, whereas that of scarlet fever affects the skin and kidneys. Moreover, in scarlet fever the organism, owing to its invasive property, may extend from the local lesion and involve other structures. It may spread to the local cervical glands, or along the Eustachian tube to the middle ear. In rare instances it extends down the respiratory tract to the lungs, or enters the blood stream to be deposited in distant structures, such as bones, joints and kidneys.

It is of the utmost importance to realise that in children there may be a gross abnormality of the fauces without complaint of sore throat. This is more frequent in cases of diphtheria than of scarlet fever. In the latter sore throat is a much more consistent symptom and is usually a more prominent one, as the pain is greater. *Dysphagia*—pain on swallowing—is a common accompaniment of sore throat. Occasionally sore throat produces a referred pain in the ear, which on examination is found to be normal. It cannot be too strongly emphasised that the throat of every sick child should be examined.

Acute Coryza.—Although the symptoms of this condition are mainly nasal—an acute nasal catarrh—the pathological process is a rhinopharyngitis. Acute coryza is a feature of many infectious diseases; in the common cold it is the principal manifestation, but in other diseases merely one of several. Measles is the most important example. Coryza occurs, but not so prominently, in rubella, whooping-cough, influenza, facial erysipelas, etc.

At the beginning there is usually sneezing, but the chief manifestation is nasal discharge. The nasal mucosa is injected and swollen. The discharge, at first thin and "watery," later becomes mucopurulent and more profuse. It may cause excoriation of the nostrils and upper lip. The inflammation often involves the nasal and lacrymal ducts and the eyes—causing conjunctivitis with injection and discharge. The congestion of the nasopharyngeal mucosa may obstruct the orifice of the Eustachian tube. The process may spread up the Eustachian tube to the middle ear, or down the respiratory tract to the lungs. Sometimes the nasal sinuses are involved. Diphtheria of the nose, although exhibiting some symptoms of coryza, usually has distinguishing features of its own. The discharge is often blood-stained, and membrane can sometimes be seen within the anterior nares.

Cough.—Any inflammatory processes involving the respiratory tract from the pharynx downwards may result in coughing.

The symptom occurs in a number of infectious diseases, notably in measles, whooping-cough, influenza, laryngeal diphtheria and pneumonia. The nature of the cough may be distinctive. There is the short, dry cough of measles and pneumonia, the barking, " croupy " cough of laryngeal diphtheria, the paralytic cough of the late stages of pharyngeal diphtheria and the spasmodic cough of pertussis. In adults coughing is associated with expectoration, but children usually swallow their sputum.

Cough, however, is merely one of the abnormal " noises " heard during respiration. The following is a list of the common " noises " which may be met with in fever practice, grouped according to the stage of respiration in which they occur :—

1. DURING INSPIRATION :

Whoop—In pertussis.
Crow—In laryngismus stridulus.
Stridor—In laryngeal obstruction, *e.g.*, laryngeal diphtheria.
Snore—In enlarged adenoids, etc.

2. DURING EXPIRATION :

Cough—(Simple, spasmodic, croupy, etc.)
Grunt—In pneumonia ; usually associated with *inverted breathing*, in which the position of the pause in the respiratory cycle alters ; the usual sequence :—*inspiration, expiration, pause,* becomes :—*grunting expiration, inspiration, pause.*
Wheeze—In asthma, severe serum reaction and bronchitis with spasm.

3. THROUGHOUT RESPIRATION :

Stridor—In severe laryngeal diphtheria, enlarged tracheo-bronchial glands, etc.

The voice and cry, both expiratory actions, may also have characters which assist diagnosis. There may be hoarseness or aphonia in laryngitis (including laryngeal diphtheria), a nasal quality to the voice in diphtheritic paralysis of the palate or pharynx and in retropharyngeal abscess, a sharp nocturnal cry in meningitis, and a peculiar and characteristic cry in retropharyngeal abscess which has been likened to the quack of a duck.

Broncho-pneumonia.—The involvement of the respiratory tract becomes serious when the inflammatory process extends,

as it sometimes does, to the lung substance, producing patches of consolidation around the terminal bronchioles. This condition of *broncho-pneumonia* is one of the two commonest causes of death in infectious diseases, the other being heart failure from toxæmia. Broncho-pneumonia occurs as a complication of whooping-cough, measles and influenza—in which diseases it is the usual mode of death—and occasionally in diphtheria, enteric fever, scarlet fever, etc., although in these death, when it occurs, is more commonly the result of heart failure. In contrast to acute (lobar) pneumonia, which is a primary and specific disease due to the pneumococcus, broncho-pneumonia is usually a secondary spread from the upper respiratory tract and may be caused by a number of different organisms. In the infectious diseases, however, it is most commonly caused by the hæmolytic streptococcus, *e.g.*, in measles, a virus disease, the broncho-pneumonia, which not infrequently complicates it and which is responsible for most of the deaths, is due to a hæmolytic streptococcus.

When broncho-pneumonia occurs in the infectious diseases it may appear during the early stages of the illness, or it may be deferred until the second or third week. In the former case the temperature, instead of falling, remains raised; in the latter an apyrexial period usually intervenes. The complication is more likely to appear in those who have had previous attacks of bronchitis or broncho-pneumonia. It may start as an inflammation of the larger bronchi and gradually extend to the finer tubes and lung substance, or it may involve the whole bronchial tree and air vesicles simultaneously. The inflammation of the lung substance results in the appearance of patches of consolidation, due to exudation of cells and fluid into the alveoli. Both lungs are affected, but the bases are usually most extensively involved, and one side is often more affected than the other. The patches may be small, discrete and scattered, or so large or so closely set as to coalesce, producing an extensive, almost uniform, area of consolidation. This is more likely to occur at the bases than elsewhere. The more extensive the consolidation, the greater the amount of lung put out of action and the more severe the symptoms. Interspersed between the areas of consolidation are small patches of collapse, and this also diminishes the amount of functioning lung tissue. Occasionally a severe form of broncho-pneumonia occurs in which consolidation is insignificant. The most striking feature is an inflammation of the fine tubes, a *bronchiolitis*. This type is frequently fatal.

DIAGNOSIS.—The onset of broncho-pneumonia is usually

gradual. The three main symptoms are pyrexia, cough and dyspnœa.

The *temperature* is usually high and remittent, *e.g.*, 100° to 104° F. or more, although cases occasionally occur in which the pyrexia is insignificant. The pulse is always rapid. At the beginning of the disease it may be full, but later it becomes soft. *Cough* is constantly present and is often distressing. In the worst type of case it may become feeble.

When whooping-cough is complicated by broncho-pneumonia the typical whoop is sometimes lost, particularly in weakly infants.

Dyspnœa—difficulty in breathing—manifests itself in rapid respirations, recession of soft parts, prostration of varying degree and, in the worst cases, cyanosis. In the mildest cases the rate of respiration is about 40 per minute ; usually it varies between 50 and 70 ; in the worst cases it may rise to 100 or more.

Respiration is more often shallow than laboured. Sometimes it is inverted ; expiration is grunting and inspiration is accompanied by dilatation of the nostrils.

The recession of the soft parts during inspiration is due to deficient expansion of the lung. It involves the intercostal spaces and the supraclavicular, suprasternal and epigastric areas. Although it is sometimes so marked as to simulate the violent retraction which occurs in laryngeal obstruction, it is usually not a marked movement of the chest.

Cyanosis is a dangerous sign, not only because it indicates a measure of respiratory failure, but also because it implies an inadequacy of oxygen for the heart, already labouring under the heavy burden of the disease. Some degree of cyanosis is present in most severe cases. When slight it involves the lips or distal parts of the extremities only ; when more severe the whole body may be of a dull leaden hue—although the blueness is most marked on the lips, face and extremities.

It cannot be too strongly stressed that it is sometimes difficult or impossible to detect any abnormal signs by auscultation of the chest, and that this state of affairs may persist for some days. Usually signs of some sort are present. At the beginning the most characteristic adventitious sounds are fine râles or crepitations localised to the bases, where the breath sounds are feebler than normal. Elsewhere in the lungs coarser râles may be present. It is not until later that definite evidence of consolidation can be detected. When the areas of consolidation are sufficiently large they may cause impairment in the percussion note (not dullness), bronchial breathing

and consonating râles. During the transition from the former stage to the latter the abnormalities are often suggestive but indeterminate, and careful search of the whole chest is necessary to find an area with definite evidence of consolidation. The larger the patch and the nearer it is to the surface of the chest, the more easily can it be found ; and, per contra, the smaller it is and the more deeply embedded and enclosed by healthy lung, the more difficult it is to detect. Sometimes the only abnormality over an area of extensive consolidation is the feebleness or absence of breath sounds. Although the detection of a definite patch of consolidation is extremely helpful, the frequency with which it cannot be elicited should emphasise the danger of depending upon this manifestation for making the diagnosis, especially in measles.

It occasionally happens that because one lung is less affected than the other, abnormal physical signs cannot be detected on one side of the chest. This may confuse the diagnosis.

When in doubt, radiological examination should be employed. Patches of consolidation appear as ill-defined areas of faint opacity.

COURSE.—As a rule the activity of the disease, as evidenced by the pyrexia, lasts one to three weeks, but duration is very variable. Occasionally, as in the influenza epidemic of 1918-19, the condition proves rapidly fatal, patients dying in twenty-four to forty-eight hours and before consolidation can occur. At the other extreme is the protracted form of broncho-pneumonia, not uncommon in whooping-cough and measles, in which the fever continues for several weeks. The consolidation gradually spreads until a large part of both lungs is involved, and the prolonged illness produces a progressive wasting of the patient. During the course of the severer types of broncho-pneumonia, acute exacerbations with cyanosis and collapse not infrequently occur and may prove fatal.

If a patient with broncho-pneumonia is not to recover, pyrexia, dyspnœa and cyanosis increase, the constitutional symptoms become more severe, with restlessness and sleeplessness. The pulse becomes thready, the cough reflex depressed, the lungs filled with râles from the accumulation of secretions and the patient dies of respiratory failure.

If recovery is to occur the pyrexia usually subsides by lysis—*cf.* lobar pneumonia. Constitutional symptoms improve gradually ; the cough abates ; the respiratory distress diminishes ; the patches of consolidation slowly resolve and

the signs in the lungs clear up. Convalescence is slow and is liable to be interrupted by one or more relapses.

PROGNOSIS.—The younger the patient the worse the prognosis. Debilitated children do badly. Cases with a high remittent temperature are usually severe. The more extensive the consolidation and the more severe the dyspnœa, the more grave is the prognosis. The fatality rate in children in fever hospitals with broncho-pneumonia is about 20 to 40 per cent. Although death is usually due to respiratory failure, it may result from heart failure or exhaustion. Sometimes diarrhœa and vomiting complicate the picture and render the prognosis much graver.

Another important feature of the disease is the liability to *permanent* damage of the lung. In broncho-pneumonia not only is the lung parenchyma involved, but so also is the interstitial tissue. Occasionally, after the temperature subsides some signs persist—usually a few râles at the bases associated with poor entry of air and continuation of the general cachexia. The persistent low-grade interstitial inflammation then results in fibrosis of the lungs. Sometimes no clinical evidence of this can be detected. It is therefore important to control the progress of the case by repeated radiological examinations. Fibrosis is more likely to follow cases with relapses, recurrent cases and in the protracted type of the disease.

TREATMENT.—Broncho-pneumonia complicating infectious diseases such as measles and whooping-cough is believed by some clinicians to be transmissible to uncomplicated cases. It is therefore desirable, where facilities are available, to isolate patients. Nursing is a measure of the utmost importance. An abundance of fresh air is essential. The room should be well ventilated or the patient placed near an open window, but not allowed to get cold. The patient, although kept at rest in bed, should not be permitted to lie for hours in one position, but should be frequently moved. As a rule, dyspnœa is relieved by propping the patient up, but the position which appears most comfortable and therefore most restful is the most suitable. Diet should be milk and fluids with added glucose, given in small quantities at frequent intervals (see p. 88). Most clinicians agree that alcohol (usually brandy) is helpful in severe cases, but it should not be used indiscriminately. For an infant of one year doses of 10 to 30 minims three or four times a day are adequate. Counter-irritants to the chest, such as linseed poultices, antiphlogistine (cataplasma kaolini) or camphorated oil, often help. Care must be taken not to burn the skin. A simple pneumonia jacket of gamgee tissue is often enough.

Only if hyperpyrexia (105° F. or more) occurs should attempts be made to reduce the temperature. The only suitable method is hydrotherapy (graduated tepid baths for infants, cold packs or sponging for older children). Antipyretic drugs should never be used. Restlessness and loss of sleep may be controlled by tepid sponging, bromides or phenacetin.

Drugs are probably of little value. Three types are used :—

(i) *Expectorants*, to increase and loosen secretions : unsuitable, particularly in infants and serious cases.
(ii) *Belladonna or atropine*, to dry up the secretion and prevent the patient drowning in his own secretion.
(iii) *Stimulants*—strychnine, adrenalin, coramine, etc.

If cyanosis is present and unrelieved the prognosis is invariably grave. Oxygen should be administered, either nasally or by means of an oxygen tent, and may need to be given over many days.

When convalescence is established, fresh air, ultra-violet light, tonics and a restorative diet (see p. 87) should be continued for several weeks.

The Middle-Ear Cleft and Otitis Media

One of the commonest complications of the inhalation diseases is the spread of the inflammatory process from the nasopharynx to the middle ear. The middle-ear cleft, comprising the Eustachian tube, middle ear, aditus, mastoid antrum and cells, is lined by mucosa which is directly continuous with that in the pharynx. It is usual to regard inflammation of the middle-ear cleft as occurring in three successive stages, at any one of which the process may be arrested : firstly Eustachian catarrh, then otitis media, and lastly mastoiditis. As far as infectious diseases are concerned, it is wiser to regard every infection as involving the *whole* of the middle-ear cleft in a catarrhal process, which may go on to suppuration in one anatomical region only, *e.g.*, the middle ear. Actually the brunt of most infections of the cleft does fall upon the middle ear, hence "acute otitis media" is the commonest clinical manifestation of such infections. The complication occurs most commonly in measles and scarlet fever, but is seen in almost all infectious diseases, including whooping-cough, infectious sore throat, influenza, acute coryza, diphtheria, cerebrospinal meningitis and typhoid fever. It is vitally important to realise that in almost every instance, no matter what the primary disease, the causative organism of

the otitis media is a hæmolytic streptococcus acting in most cases as a secondary invader.

The younger the patient the more likely is otitis media to occur as a complication. This is attributed to the shortness and straightness of the Eustachian tube of the child, permitting infection to pass more easily from the pharynx to the middle-ear cleft.

Any pre-existing abnormality of the upper respiratory tract or of the cleft increases the chances of the complication occurring, *e.g.*, patients who have had a previous attack of otitis media are very liable to get a recurrence if they develop scarlet fever.

The condition may be unilateral or bilateral. Both sides may be affected simultaneously, or one side may follow on the other after a variable interval.

Although an acute otitis media occasionally remains catarrhal, in the vast majority of cases suppuration occurs. The mucopurulent discharge accumulates in the middle ear and may escape through a spontaneous perforation of the tympanic membrane. This may occur within a few hours of the onset, or be delayed for some days unless in the meantime the drum-head has been incised by the surgeon.

The three most important symptoms of acute otitis media are pyrexia, otalgia (pain in the ear) and otorrhœa (discharge from the ear), but they are not always present. In children particularly there is considerable variability, not only as regards the intensity of the symptoms, if present, but also as regards their combination. Pyrexia is usually sudden in onset and is associated with a varying degree of general disturbance —malaise, anorexia, nausea and vomiting. The temperature usually ranges between 100° and 103° F. and runs an irregular remittent course. Sometimes it is the only symptom. Acute otitis media is, in fact, one of the commonest causes of unexplained pyrexia in children. Symptoms referable to the ear commonly occur after two or three days of illness, but sometimes they are present from the onset. In older children pain in the ear is always definite and often severe, but in younger children it may be insignificant or the patient may not be old enough to complain. Occasionally in such children attention may be directed to the ear because the patient refuses to lie on the affected side on account of the tenderness accompanying the inflammation. When the discharge appears the pain and the pyrexia usually abate. The otorrhœa may commence within twenty-four hours of the onset of symptoms or may be delayed for as long as seven days or more. In young

children, particularly if debilitated, otorrhœa is occasionally the first and only symptom.

The discharge is at first thin, clear, seromucous and small in amount; later it becomes thicker, mucopurulent and more profuse.

Uncommon symptoms in children are noises in the ear and some deafness.

The SIGNS OF ACUTE OTITIS MEDIA are tenderness in the region of the ear and changes in the drum-head. Tenderness is not uncommon before the discharge appears, but usually subsides when the otorrhœa is established. It may be present in front of or behind the ear, or there may be hypersensitiveness of the whole of the ear and even of the side of the face. Changes in the drum-head are invariably present in the form of an inflammation of the tympanic membrane with loss of the usual landmarks—particularly the light reflex and the handle of the malleus. The redness and swelling may be localised, *e.g.*, to the posterior half, or may involve the whole drum-head. The red and bulging drum ultimately ruptures. The perforation is not always visible, but its existence can be assumed if *pulsation of the drum-head* is seen communicated to a little discharge at the bottom of the auditory canal.

TREATMENT.—If the drum-head is unruptured the operation of *myringotomy* (incision of the tympanic membrane) should be performed. During the pyrexial period local heat is of value. The discharge should not be allowed to accumulate in the auditory canal, but should be mopped away frequently and spirit or antiseptic drops (*e.g.*, glycerin of carbolic, 5 per cent.) instilled. Pain and sleeplessness may demand the exhibition of analgesics and hypnotics.

Recently the sulphonamide group of drugs has been used in the treatment of streptococcal infections of the middle-ear cleft with encouraging results.

COMPLICATIONS—*Mastoiditis*.—Sometimes the suppurative process extends to the mastoid antrum and cells. This complication may arise acutely or be so insidious in its onset that its existence is suspected only because the infection persists for an unusually long time, *e.g.*, more than three or four weeks. Acute mastoiditis may manifest itself early, *i.e.*, shortly after the onset of the ear trouble, and whilst there is still pyrexia from the otitis media; or an apyrexial period may intervene between the otitis media and the mastoiditis. The chief manifestations (which are not invariably present) are pyrexia, changes in the discharge, which may become more profuse or be suppressed, pain and tenderness over the mastoid process,

the appearance of a swelling behind the ear which may cause the pinna to stand out from the head and the posterior meatal wall to bulge, and deafness.

Surgical treatment is almost invariably required, usually the simple mastoid operation of Schwartze, in which the cortex of the mastoid process is taken away to permit removal of diseased bone and mucosa and to allow free drainage of the antrum.

OTHER COMPLICATIONS.—In rare instances the inflammation of the middle-ear cleft extends to intracranial structures, producing such serious complications as meningitis, extradural, cerebral or cerebellar abscesses, and thrombosis of the lateral sinus. They are most likely to occur if treatment of an acute mastoiditis is unduly delayed.

SUMMARY OF CHAPTER VI

Sore Throat: Particularly in scarlet fever and diphtheria.

Acute Coryza: Particularly in measles, rubella, whooping-cough and influenza.

Cough: Short and dry in measles and pneumonia; croupy in laryngeal diphtheria; paralytic in paralysis of the pharynx (diphtheria); spasmodic in whooping-cough.

Abnormal "Noises" during—

(*a*) Inspiration: Whoop, crow, stridor, snore.
(*b*) Expiration: Cough, grunt, wheeze.
(*c*) Throughout respiration: Stridor.

Broncho-pneumonia (usually Streptococcal): Pyrexia, cough, dyspnœa, patchy consolidation.

Acute Otitis Media (Suppurative): Pyrexia, otalgia, otorrhœa.

CHAPTER VII

DIAGNOSIS (CONTINUED)

III. RASHES

THE cutaneous picture to which the name *rash, eruption* or *exanthem* is given is produced by the action of an organism or its toxic products on the skin, or, more correctly, upon the small blood vessels of the skin. A rash is a clinical feature of many infectious diseases, and is often so typical or specific as to be an important diagnostic sign—almost *pathognomonic.* In one group of diseases, the *exanthemata,* a specific rash is the rule, *e.g.,* scarlet fever, measles, rubella, chickenpox, smallpox, etc. In a second group rashes do not occur, *e.g.,* diphtheria, whooping-cough, etc. In a third group a specific rash may or may not occur; its presence is of assistance in diagnosis, but its absence does not exclude the disease, *e.g.,* enteric fever.

Occasionally diseases belonging to one or other of these groups show deviations from the rule. Exceptionally exanthemata are seen without the rash, *e.g.,* measles without its characteristic eruption. The rash fails to appear because the disease is exceptionally mild, or because it is so severe that the patient's skin fails to respond, or because the skin is resistant. In some diseases, *e.g.,* smallpox, if the infection is overwhelming the patient may die before the characteristic rash appears. On the other hand, diseases without a rash, such as diphtheria and whooping-cough, sometimes show cutaneous lesions (hæmorrhages), although the eruption is not specific as it is in the exanthemata. Such hæmorrhages usually indicate a severe attack.

Since the rash is such an important diagnostic sign, its examination should be carried out carefully. The whole of the body should be examined and an opinion should not be given if the examination cannot be conducted in a good light —preferably daylight. Attention should be paid to the type of rash, its colour and distribution, where it was first noticed and whether it is associated with subjective symptoms, such as itching.

A. Distribution of Rashes

Before considering the *details* of a rash it is most important to decide *first* which areas of the skin are affected, *i.e.*, its distribution. Most of the rashes occurring in the infectious diseases are *generalised*. But when the rash is fully out it may be found that the lesions are not uniformly distributed over the skin, and some places may escape entirely. This distribution implies consideration of—

(*a*) *Absolute distribution*—those areas which are affected and those which are free.

(*b*) *Relative distribution*—comparison of the *profuseness* of the rash in the parts which are affected.

Moreover, different diseases behave differently as regards the place and manner in which the rash appears, evolves and disappears, and in the general profuseness of the spots. All these points are of assistance in diagnosis.

Site at which the Rash First Appears.—As a rule rashes first appear in the upper part of the body (usually around the head and neck) and spread downwards with varying rapidity. The trunk is usually involved before the extremities, and the last areas to be affected are usually the distal parts of the lower limbs. Usually the spread is so rapid that the lesions seem to have appeared simultaneously. Sometimes, with the more slowly spreading rashes, cases are seen before the eruption is generalised. It is therefore important to know the sites at which the various rashes *first* appear. The rash of measles, for example, first appears on the forehead and neck, and a rash which starts on the legs without any involvement of the face is unlikely to be due to measles.

Absolute Distribution.—The *absence* of the rash from any region of the body may be due to the fact that that part is not usually involved, *e.g.*, the axillæ in smallpox ; or that the eruption is not fully out, *e.g.*, the extremities, and even the trunk, in an early case of measles ; or that the rash has disappeared from that part of the body, *e.g.*, the face in late rubella.

Profusion of the Rash.—The profuseness of the lesions varies considerably in different diseases and in the same disease in different patients. The rose-spots of enteric fever are almost invariably sparse, whereas the rash of measles is usually profuse. In many diseases the rash is sparse at the beginning and becomes profuse later. A good example is the

rash of chickenpox, which comes out in "crops," so that at the beginning there are very few lesions ; later on there may be many more.

Note should also be made as to whether the individual spots of a rash are *discrete, i.e.*, quite separate, or *confluent, i.e.*, several running together. Confluence is the rule in measles and the exception in chickenpox. A rash may be discrete in one part of the skin and confluent on another, *e.g.*, smallpox may be confluent on the face and discrete on the body.

Relative Distribution.—In determining the relative distribution of a rash it is necessary to compare the abundance of the lesions on the various anatomical regions. The relative distribution of the rash is one of the most important diagnostic points in differentiating smallpox from chickenpox (see Figs. 27 and 28).

Certain local factors may influence the profuseness of a rash. A site of local inflammation or irritation may result in a local profusion of spots.

Disappearance of the Rash.—The rash may fade and disappear uniformly, or disappear in the same order in which it appeared, *i.e.*, from above downwards. It sometimes happens, therefore, that the rash will have gone from the first area affected, *e.g.*, the face, whilst still present on the later parts affected, *e.g.*, lower extremities.

Enanthemata.—Specific eruptions are not necessarily confined to the skin. Mucous membranes may be affected, *e.g.*, in scarlet fever, measles and chickenpox, and these lesions on the mucosa, the *enanthem*, appear as a rule earlier and in some instances more constantly than those in the skin. Their existence may be of considerable assistance in diagnosis, and the observable mucous membranes, particularly the mouth, should always be examined.

B. Types of Primary Lesions Forming the Rash

A rash usually consists of a number of primary elements or " spots " (of which there are different sorts) grouped and arranged in various ways. The following is a list of primary elements found in infectious diseases :—

(i) *Erythema :* A uniform redness of the skin.

(ii) *Punctum :* A minute, almost pin-point, spot of redness or hæmorrhage.

(iii) *Macule :* A small round, red spot, about the size of a freckle, not raised above the surface of the surrounding skin.

(iv) *Papule:* A small round spot, of the same size as a macule, slightly raised above the surface of the surrounding skin and therefore palpable.

(v) *Vesicle:* A small raised spot containing clear fluid; a small blister.

(vi) *Bulla or bleb:* A larger lesion containing fluid.

(vii) *Pustule:* A small raised spot, about the size of a vesicle, but containing purulent fluid. Most vesicles become pustules in time.

(viii) *Urticaria or wheal:* A localised effusion of fluid into the skin, causing a raised, white or whitish-pink area with a halo of erythema. Wheals vary in size; they never rupture as do vesicles, bullæ and pustules.

(ix) *Nodule:* A raised solid lesion, larger than a spot.

Other terms used are :—

(x) *Hæmorrhage:* Escape of blood into the skin; may be in spots (*punctate hæmorrhage* or *petechia*) or in larger extravasations.

(xi) *Pigmentations or staining:* Coloration of the skin, usually following the extravasation of blood, from which the pigment is derived.

(xii) *Desquamation or peeling:* Dry scaliness of the skin due to flaking of the upper layers of the epidermis.

(xiii) *Scab:* A crust of dried-up fluid and epidermal debris covering a cutaneous lesion, such as a ruptured vesicle, bulla or pustule.

(xiv) *Scar:* A depressed permanent blemish due to destruction of deeper parts of the epidermis.

Types of Rashes.—Rashes are composed of one or more primary skin lesions; if the elements are all of the same character the rash is *monomorphic*; if two kinds are present, *dimorphic*; if more than two, *polymorphic* or *pleomorphic*. In some diseases, *e.g.*, measles, the rash is monomorphic throughout. In others the rash starts off as one element and evolves into others, *e.g.*, in chickenpox and smallpox the rash starts as macules which become papules, vesicles and pustules. But in chickenpox, owing to the tendency for fresh crops to come out and evolve quickly, several types of lesions are present at the same time, *i.e.*, the rash is polymorphic; in smallpox the evolution is slower and at any stage the lesions are monomorphic, or at most dimorphic.

In many rashes occurring in infectious diseases the colour

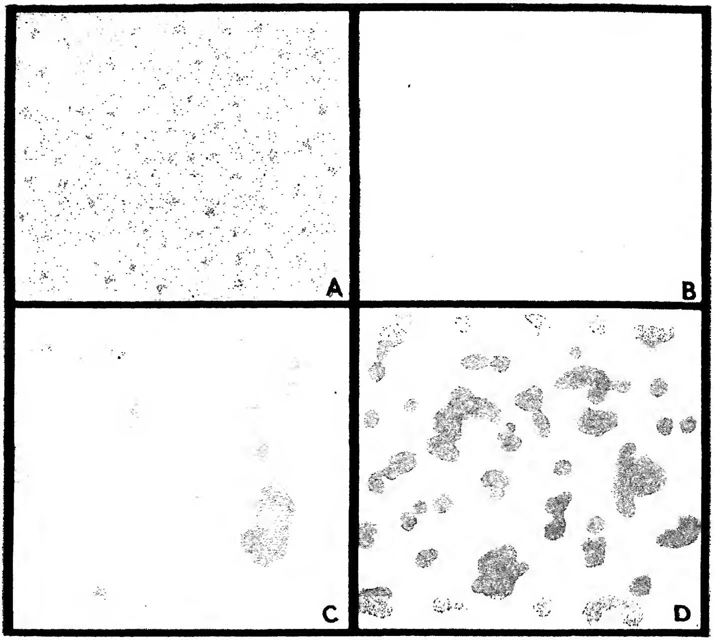


FIG. 6.—Types of Rashes.

A : Scarlatiniform—punctate erythema.
B : Roseoliform—discrete pink macules.
C : Pleomorphic, *e.g.*, in serum disease, showing macules, erythematous, circinate and gyrate patches. The common urticarial wheal is not illustrated.
D : Morbilliform—fusing maculo-papules forming dull red blotches.

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depends upon vascular dilatation alone, so that on pressure the colour disappears. Such rashes are known as *erythematous*. The commonest types are :—

(i) *Scarlatiniform erythema* (punctate erythema): The typical rash of scarlet fever. There is an underlying erythema with superimposed points or puncta of greater intensity. The colour is bright red.

(ii) *Morbilliform erythema:* The typical rash of measles. It consists of macules, or maculo-papules, which have grouped themselves together and coalesced into patches, "blotches," crescents, etc., with normal skin between. The colour is dusky red.

(iii) *Roseoliform erythema:* The typical rash of rubella. It consists of discrete macules of a rose-pink colour.

(iv) *Urticarial or erythemato-urticarial rashes:* The typical eruption in serum disease. The rash consists of patches of erythema, irregular in shape and size, in the centre of which a wheal usually, but not invariably, appears. The size of the wheal relative to the halo of erythema varies considerably.

Hæmorrhage into the Skin.—Since hæmorrhages are due to the escape of blood from the vessels, they do not disappear on pressure, as do the erythematous rashes, which are due merely to vascular dilatation. In infectious diseases, hæmorrhages when they occur are usually small—*punctate hæmorrhages*, *purpuric spots* or *petechiæ*. Large extravasations occasionally occur.

The hæmorrhagic manifestations may be classified as follows :—

(i) *Hæmorrhagic Rashes.*—The hæmorrhages occur into the specific rash of the disease, implying that the usual vascular dilatation has advanced to a stage permitting the escape of blood. In smallpox such an occurrence indicates a severe attack of the disease, but in scarlet fever and measles it merely indicates a severe rash, not necessarily a severe attack of the disease. (The hæmorrhages in scarlet fever are usually localised petechiæ, *e.g.*, to the flexures of the elbows (Pastia's sign).)

(ii) *Hæmorrhages in Toxic Cases.*—In severe toxic cases of infectious disease, whether exanthemata or not, hæmorrhages into the skin may occur. They may be petechial or larger extravasations. Examples occur in diphtheria, cerebrospinal meningitis and

smallpox. In the exanthemata the petechiæ appear before the true rash, *i.e.*, as a prodromal rash (see below). Such cases are almost invariably fatal.

(iii) *Mechanical hæmorrhages*, petechiæ or larger extravasations, occur in whooping-cough. They are due to rupture of small vessels during the intense congestion set up by severe spasms of coughing.

OTHER TYPES OF ERUPTION occasionally seen are :—

(i) *Herpetiform rashes*, consisting of localised *groups of closely set vesicles* on an erythematous base, *e.g.*, simple herpes of the face and herpes zoster.

(ii) *Circinate rashes*, consisting of circular or oval patches of erythema with a more intense margin due to fading in the centre.

(iii) *Gyrate rashes*, irregular areas of erythema with scalloped margin of greater intensity, due to fading in the centre.

Both circinate and gyrate lesions occur in serum disease and in toxic rashes due to drugs, etc.

PRODROMAL RASHES.—Prodromal rashes, seen occasionally in the exanthemata, are eruptions which appear before the true or specific rash. They are of two main types :—

1. *Erythematous*—either scarlatiniform, morbilliform or urticarial, usually transient and disappearing before the true rash comes out.
2. *Petechial*—usually denoting a severe and possibly fatal attack (see Hæmorrhagic Rashes). If the patient does not die before the true rash appears, the petechiæ may be detected mixed with the characteristic lesions. Care should be taken to distinguish flea-bites, with their central *punctum*.

Diseases in which prodromal rashes are occasionally seen :—

Smallpox : Erythematous or petechial.
Chickenpox : Scarlatiniform.
Measles : Erythematous.

Itching or Pruritus in the Exanthemata.—Most of the exanthemata do not itch, and this is a useful diagnostic point. It is not invariably so ; scarlet fever and chickenpox, for example, occasionally itch. On the other hand, in some conditions confused with infectious diseases itching is the rule, *e.g.*, scabies and papular urticaria, the latter particularly being

	Elementary Lesions	Colour	Distribution	Remarks
Erysipelas .	ERYTHEMA ($\pm$BULLÆ)	BRIGHT RED	LOCALISED PATCH, *e.g.*, FACE	RAISED MARGIN.
Scarlet Fever	ERYTHEMA + PUNCTA	BRIGHT RED	GENERALISED EXCEPT FACE	DESQUAMATION AFTER THE RASH DISAPPEARS.
Rubella .	MACULES	PINK	GENERALISED: DISCRETE	...
Measles .	MACULES (OR MACULO-PAPULES)	DULL RED	GENERALISED: CONFLUENT, PRODUCING BLOTCHES	SLIGHT DESQUAMATION AND STAINING AFTERWARDS.
Enteric .	PAPULES (OR MACULO-PAPULES)	ROSE PINK	USUALLY TRUNK	FEW IN NUMBER.
Chickenpox .	MACULES, PAPULES, VESICLES, PUSTULES, CRUSTS, SCARS	...	GENERALISED: CENTRIPETAL	TENDENCY TO PLEOMORPHISM. FAINT SCARS AFTERWARDS.
Smallpox .	*Ditto*	...	GENERALISED: CENTRIFUGAL	TENDENCY TO BE AT SAME STAGE. PITTED SCARS AFTERWARDS.
Serum Rash .	ERYTHEMA + URTICARIA (SOMETIMES OTHER TYPES)	WHITE WHEAL WITH PINK AREOLA	BLOTCHES AND PATCHES: LOCAL OR GENERALISED	...
Erythema Nodosum	NODULES	PURPLISH RED	SHINS	...
Impetigo .	VESICLES OR BULLÆ + CRUSTS	CRUSTS: AMBER	MAINLY FACE	...

important as it is frequently confused with chickenpox. The rash of secondary syphilis, which has always to be borne in mind in adults, does not itch.

It is important to realise that the rash is rarely the only sign of the disease. A diagnosis of scarlet fever or measles, for example, should never be made on the rash alone. In some diseases, *e.g.*, rubella and chickenpox, the rash is sometimes the only manifestation.

SUMMARY OF CHAPTER VII

Most important points to consider in diagnosing rashes :—

Distribution—absolute and relative.
Site at which rash first appears.
Type of primary lesions.

Types of Rashes :

Erythematous—
(i) Scarlatiniform.
(ii) Morbilliform.
(iii) Roseoliform.
(iv) Urticarial.

Hæmorrhagic.
Prodromal : Erythematous, hæmorrhagic.

CHAPTER VIII

DIAGNOSIS (CONTINUED)

IV. ACCESSORY AIDS

WHEN clinical evidence is insufficient to permit a diagnosis to be made, assistance may often be obtained from ancillary examinations. These usually take the form of tests performed either in the ward upon the patient or in the laboratory upon material obtained from the patient. These tests are also used to confirm a diagnosis made on clinical grounds. It is important to realise at the outset that no biological test is accurate in 100 per cent. of cases. The information provided by the test must be used as additional evidence only. A diagnosis of **disease** should *never* be made from tests alone ; the ultimate decisions must be made on *clinical* grounds. The *accessory methods* of diagnosis can be considered under the following headings :—

Bacteriological Methods.—All the infectious diseases are due to specific micro-organisms. A search for the suspected organism at the right time and in the right place frequently reveals its presence. Diphtheria bacilli are found on swabbing the site of local membrane formation in diphtheria ; typhoid or paratyphoid bacilli can be detected in the blood, stools and occasionally the urine in enteric fever ; hæmolytic streptococci are present in the fauces in scarlet fever ; the meningococcus is found in the blood and cerebrospinal fluid in cerebrospinal meningitis ; the hæmophilus pertussis may be isolated from the droplets expelled during a paroxysm of coughing in whooping-cough ; and there are many other examples mentioned under the individual diseases. The method obviously cannot be applied where the causative organism is unknown, or cannot be detected by the ordinary bacteriological methods, *e.g.*, in measles, rubella, mumps, etc. In most of the infectious diseases the organisms are most profuse, and can therefore be most readily detected in the early stages of the disease. In the course of a few days or weeks, depending upon the disease, the organisms disappear. The later the patient comes under examination, the less reliable is this method.

There is another serious fallacy in this method of diagnosing disease by searching for the causative organism. It is a test of *infection,* not a test of disease. The difference between infection and disease has already been stressed (p. 7). Infection may occur in individuals who are immune to the disease (carriers) and those who have a latent infection. In such cases the mere *presence* of the causative organism does not imply the existence of *disease, e.g.,* diphtheria bacilli.

Immunological Methods.—In the description of Infection and Resistance (Chapter II, p. 7) it was shown that—

1. Disease occurs only in susceptible individuals.
2. Disease always results in some reaction on the part of the protective mechanism of the body, with the production of specific antibodies in the blood and tissues.
3. On recovery from the disease the patient is usually immune.

If, then, we test the immunity reactions of an individual suspected to be suffering from the disease and find him passing through these stages, it is obvious that he is actively producing specific antibodies. It is therefore a reasonable inference that he is infected with the organism in question, and therefore is suffering from the disease. It is rarely possible to follow every stage immunologically. Sometimes we examine for stage 2, *i.e.,* the active production of antibodies ; sometimes for stages 1 and 3, *i.e.,* for susceptibility at the beginning and immunity at the end ; sometimes we must be content with stage 1 only. Representative examples are given below :—

(i) EXAMINATION FOR THE ACTIVE PRODUCTION OF ANTIBODIES—WIDAL TEST.—In enteric fever specific agglutinins appear in the blood and can be detected by the Widal test after about the tenth day. If, therefore, a patient suspected to be suffering from enteric fever develops a positive Widal reaction, the diagnosis is confirmed. (For more detailed interpretation of the Widal reaction see Enteric Fever, Chapter XXX, p. 377.)

(ii) EXAMINATION FOR SUSCEPTIBILITY AT THE BEGINNING AND IMMUNITY AT THE END—DICK TEST.—At the beginning of an attack of scarlet fever the Dick test is positive, indicating susceptibility to the disease. In the course of the illness specific antitoxins are produced, and after about three weeks the Dick

test becomes negative, indicating immunity. If in a patient suspected to be suffering from scarlet fever the Dick test changes from positive to negative, it can be inferred that he has suffered from the disease.

(iii) TESTS FOR SUSCEPTIBILITY AT THE BEGINNING—SCHICK AND DICK TESTS.—At the beginning of an attack of diphtheria the Schick test is positive, indicating susceptibility. If a patient suspected to be suffering from diphtheria is examined early in the disease and found to be Schick negative, it is strong presumptive evidence against the diagnosis. If the Schick test is positive it does not mean that the patient *is* suffering from diphtheria. It merely means that it is possible for him to do so. Whether he is suffering or not must be decided by other evidence—clinical and bacteriological. Later Schick tests are not performed because patients thought to be suffering from diphtheria are usually given antitoxin, which invalidates the test.

Similarly, the Dick test can be used only at the beginning of scarlet fever, instead of at the beginning and end as described in (ii). The same inferences are drawn as in the Schick test in diphtheria.

It is important to stress that in all the examples given above we are dealing with sick patients. Before the inferences are drawn we start off with the clinical proviso—"If the patient is suspected to be suffering from the disease . . ." The rules do not apply to healthy persons.

Immunological examinations of a different type, which are sometimes used in diagnosis, are the tests for bacterial hypersensitiveness, such as the tuberculin test. It has been pointed out that such tests are positive if the patient has been exposed to an infection (particularly a recent infection) and in consequence has developed hypersensitiveness to the specific organism. It is sometimes assumed that evidence of a recent infection can be used as evidence that the patient is suffering from the disease. The fallacies in arguing thus are obvious. The interpretation of such tests is beset with pitfalls, and each requires separate consideration.

Hæmatological Methods.—In the section on Bacteriological Methods (p. 65) mention was made of blood cultures, *i.e.*, examination of the *blood* for the detection of the causative organism of such diseases as enteric fever, meningococcal meningitis, puerperal septicæmia, pneumonia, etc. In the

section on Immunological Methods (p. 66) the various examinations of the *blood serum* for antibodies have been described. Here the changes in the circulating *cells* are considered.

As a rule the changes in the red cells are slight and not helpful. As regards the white cells in infectious diseases, the tendency is for the number to be increased (leucocytosis), due to an absolute and relative increase in the number of polymorphonuclear cells (neutrophils). Associated with this is a reduction in the number of eosinophils and monocytes. In convalescence the neutrophils return to normal, but there is a relative and absolute increase in the lymphocytes and often of eosinophils and monocytes (post-infective lymphocytosis, eosinophilia and monocytosis). Departures from this common picture occur in some diseases and can be used as an aid to diagnosis. In scarlet fever the neutrophilic leucocytosis is accompanied, not by a reduction but by an increase in eosinophils, and is the only infectious condition in which a polymorphonuclear leucocytosis and eosinophilia occur together. In whooping-cough the leucocytosis is due not to an increase of neutrophils but of lymphocytes. In glandular fever there is a considerable increase in monocytes. Sometimes a leucopenia and not a leucocytosis occurs, *e.g.*, in enteric fever. Occasionally the appearance of abnormal cells is the peculiar feature, *e.g.*, in rubella, where relatively large numbers of Türck and plasma cells appear.

The appearance of the blood is of assistance not only in diagnosis but also occasionally in judging severity, progress and prognosis. Diseases usually associated with a leucocytosis may, if they occur in a very severe form, show a leucopenia. In typhoid fever, measles and other diseases with a leucopenia the appearance of a leucocytosis suggests complications. In scarlet fever the absence of eosinophils is of grave prognostic significance.

There are difficulties in interpreting the blood picture in infectious diseases. Not the least of these depends on the fact that most patients are children, in whom the normal blood picture shows considerable variations from the adult normal. The most striking difference is a relative increase in the number of lymphocytes at the expense of the neutrophils. As the child grows the appearances gradually conform to the normal adult picture, so that there are variations at the different ages.

The Erythrocyte Sedimentation Rate (*E.S.R.*).—If an anticoagulant be added to blood the erythrocytes settle to the bottom of the container. Infective conditions (among others) produce

disturbances in the blood which cause the red cells to settle more rapidly. In normal persons the rate of settling varies between fairly wide limits, and to a certain extent age and sex influence it. Unless the rate is considerably raised, a single reading is not of much significance. If repeated and found to be rising, it suggests the continued activity of the infective process or the appearance of complications. These increased rates often coexist with pyrexia, but they may occur before the pyrexia appears, and after it has subsided. They may, in fact, be the only sign that the process is still active.

The Erythrocyte Sedimentation Rate therefore provides an additional indication of the activity of infective processes, *e.g.*, in rheumatic fever and tuberculosis. Sometimes the interpretation is difficult.

In whooping-cough the Erythrocyte Sedimentation Rate is *normal* or *retarded* and is the only acute infection in which retardation is observed.

SUMMARY OF CHAPTER VIII

Aids to Diagnosis :

1. *Bacteriological*—tests of infection.
2. *Immunological*—transition from susceptibility to immunity and tests therefor.
3. *Hæmatological*—
   (*a*) Blood for presence of organisms.
   (*b*) Blood serum for antibodies.
   (*c*) Blood counts.
   (*d*) Erythrocyte sedimentation rate.

CHAPTER IX

EPIDEMIOLOGY AND THE CONTROL OF INFECTIOUS DISEASES

EPIDEMIOLOGY is the study of the spread of infectious diseases. Those diseases which normally prevail in a country are *indigenous*; when a disease is *constantly* present in a locality it is *endemic, e.g.*, diphtheria and scarlet fever are endemic in London. If an outbreak of an infectious disease rapidly assumes considerable proportions it is *epidemic, e.g.*, epidemics of measles and influenza occur regularly in this country. An epidemic curve—a graph showing the incidence of the disease—typically exhibits a period of increase, a maximum incidence, and a period of decline (see Fig. 7). In the intervals between epidemics (*a*) the locality may be entirely free from the disease; or (*b*) *sporadic* cases may occur, *i.e.*, a few scattered cases appear with little apparent connection with each other, as in the case of cerebrospinal fever and acute poliomyelitis; or (*c*) the disease may remain endemic, like scarlet fever and diphtheria, which are *endemic diseases with epidemic phases*: the epidemic is thus a temporary and considerable augmentation of an indigenous disease. Sometimes epidemics result from the *importation* of a disease from abroad. When an outbreak of an infectious disease becomes disseminated so widely as to involve a considerable area of the globe, it is *pandemic, e.g.*, influenza in 1918-19 was world wide. This classification of the prevalence of infectious diseases is to a certain extent artificial. The distinction between "epidemic" and "pandemic," between "endemic" and "sporadic," and between "epidemic" and "endemic with epidemic phases" is largely arbitrary, but is useful to describe the behaviour of a disease at certain times and in certain places.

Fluctuations in the prevalence of infectious diseases exhibit certain regular tendencies, which may be grouped as follows :—

(i) *General Trends.*—In the course of years there may be a trend downwards or upwards, *e.g.*, diphtheria has exhibited a gradual decline in incidence in recent years.

(ii) *Periodic Cycles.*—Epidemics tend to appear at regular intervals, *e.g.*, measles and whooping-cough occur in epidemic form biennially.

(iii) *Seasonal Prevalence.*—Endemic diseases show a regular increase in prevalence at certain seasons of the year, *e.g.*, scarlet fever, diphtheria, enteric fever, and poliomyelitis in the autumn; measles, whooping-cough, pneumonia, influenza, smallpox, and cerebrospinal meningitis in the winter and early spring.

Irregular fluctuations occur from many causes, *e.g.*, population movements, the opening and closing of schools, war, spells of hot or cold weather, etc.

Many complex and variable factors are concerned in altering the prevalence of infectious diseases. The two primary factors which determine dispersability are *herd resistance* (or herd immunity) on the one hand, and the *environment of the herd* on the other. The latter includes particularly the prevalence and virulence of the causative organism. Hygiene, sanitation, overcrowding, nutrition, weather, seasonal and geographical influences, density and movement of the population merely influence one or other of the primary forces. For example, the enteric fevers, malaria, cholera, plague, etc., have been eliminated from this country by *altering the environment.* In the diseases due to droplet infection this method is unsuccessful and the alternative method of *increasing herd resistance* has to be adopted, *e.g.*, by active immunisation against diphtheria.

Herd resistance is not merely the summation of the individual immunities of the population. A herd may be immune to a disease in the sense that it will resist the introduction of the infection, although it may contain a large number of susceptibles; and another herd with the same number of susceptibles might be swept by the disease. The density of susceptibles plays a part. The susceptible population may at one part of the day be fairly evenly distributed in the herd, and later in the day it may be congregated in, say, a cinema, thereby altering its resistance. In the one case conditions may permit only sporadic cases to occur; in the other an epidemic may prevail. Again, the introduction of fresh susceptibles into the population may dilute the herd immunity to a level sufficiently low to permit epidemics to occur; or the introduction of a few additional sources of infection may alter the environment sufficiently to produce the same effect.

Infectious diseases spread not only through those who are suffering from the disease, but also through apparently healthy persons. Some are immunes, carrying the disease either chronically or temporarily; others are susceptibles with a latent infection, although their infectivity is usually short. Moreover, missed and abortive cases are not unusual. Thus, in every epidemic a much larger number are infected than fall

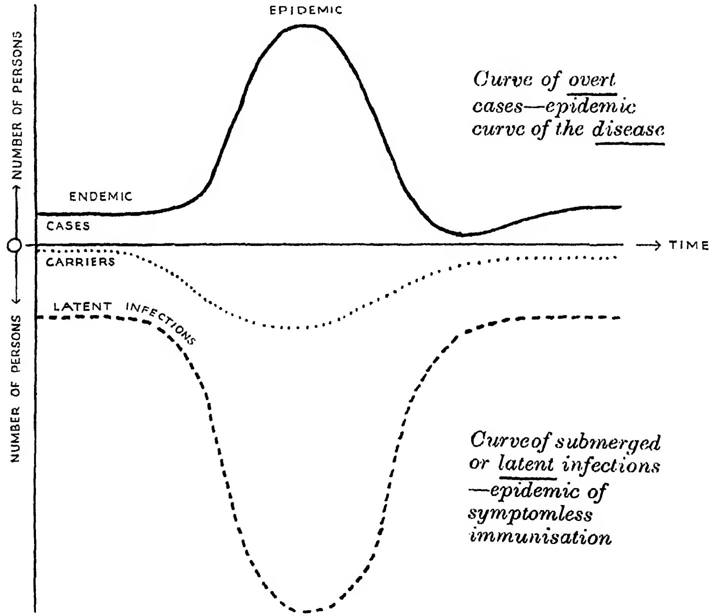


FIG. 7.—Schematic Epidemic Curves to illustrate that a much Larger Number of Persons are infected than contract the Disease, *i.e.*, the dimensions of the carrier epidemic and latent infections exceed those of the clinical epidemic.

ill or are detected. The actual cases are merely the visible evidence of an epidemic which is widespread throughout the population. Knowledge of these facts has led epidemiologists to describe "carrier epidemics" as the prelude to epidemics of the disease.

After the epidemic has been in force for some time the percentage of immunes rises and the number of susceptibles falls; and although the susceptible population is not exhausted,

the herd resistance rises sufficiently to bring the epidemic to a standstill. Other factors may contribute to this result.

In interepidemic periods chronic carriers constitute one variety of what are described as *reservoirs of infection.* If other conditions are ripe, they may set up a new outbreak.

Control of Infectious Diseases.[1]—The obvious approach to the problem of preventing the spread of infectious diseases is to remove the cause. In the present state of our knowledge pathogenic bacteria cannot be abolished. Two avenues are therefore open: to diminish as far as possible the prevalence of the organism, and to increase the herd resistance. The measures usually adopted combine both, and are enumerated below:—

A. TO DEAL WITH PATIENTS AND THEIR IMMEDIATE ENVIRONMENT.

1. Notification of cases of the disease.
2. Isolation of patients in hospital or at home.
3. Disinfection—concurrent and terminal.
4. Treatment of the patient in hospital or at home.

B. TO DEAL WITH CONTACTS.

1. Quarantine of contacts.
2. Observation of contacts.
3. Exclusion of contacts from certain places, such as schools.
4. School closure or dispersion.

C. TO INVESTIGATE THE SOURCE OF THE OUTBREAK AND IF POSSIBLE TO REMOVE IT.

D. PREVENTIVE MEASURES APPLICABLE TO THE WHOLE POPULATION.

1. Elimination of reservoirs of infection.
2. General hygienic measures to prevent the transmission of infection.
3. Protection of the susceptible population by immunisation.
4. Education and propaganda to keep the public informed and invite co-operation.

The limited value of notification and isolation in the control of infectious diseases has been mentioned in Chapter I.

[1] See also Chapter XXVII, p. 332, for more detailed account of control of ingestion diseases, and Chapter XXXVII for description of control of infectious diseases in hospital.

Terminal Disinfection, involving the disinfection of inanimate objects in the vicinity of the patient, such as the room, clothing, bedding, after the patient has recovered or been removed to hospital, is considered to-day of minor importance. Great attention is paid to *concurrent disinfection*, which is the immediate disinfection of discharges and excreta as soon as they are expelled from the body, and of inanimate objects as soon as they are infected.

Isolation is a procedure employed for *patients* or *carriers*, who are segregated in an attempt to prevent them conveying infection to other susceptible individuals.

Quarantine is a measure applied to *contacts*, *not* patients or carriers. A *contact* is a person who has been sufficiently near an infected person for infectious material to have been conveyed to him. *Quarantine* is the limitation of the free movement of contacts until it is certain that they have not acquired the disease to which they have been exposed. The period of quarantine is the longest usual incubation period of the disease. If the contact does not show signs of the disease during this period he has escaped, and can be released from quarantine. Sometimes, instead of imposing a period of quarantine, contacts are allowed to mix with others providing they are kept under medical observation during the incubation period of the disease. If symptoms appear, the contact is promptly isolated. School children who are home contacts are sometimes excluded from school; at other times they are allowed to attend but are kept under observation. School contacts in residential schools are occasionally dispersed to their own homes. The practices of exclusion, closure and dispersal are falling into disfavour.

In the *elimination of reservoirs of infection* particular attention is necessary to the control of carriers.

General hygienic measures aim at breaking the chain in the transmission of infectious diseases, *e.g.*, sanitary disposal of excreta and the provision of pure food and drink (*vide* measures for the control of ingestion diseases, Chapter XXVII, p. 332); avoidance of spraying droplets and congregating in crowded places to minimise inhalation diseases; proper housing and sanitation.

Immunisation.—Notification, isolation, disinfection and supervision of contacts—the older methods of dealing with infectious diseases—aim at eliminating sources of infection. Their failure to stop epidemics has resulted in more attention being directed to the building up of herd resistance. Of the measures employed for this purpose, one of the most important

is artificial immunisation. Unfortunately, in only a few diseases are suitable agents available, *e.g.*, smallpox, diphtheria, scarlet fever, enteric fever and whooping-cough. Although it may be desirable to protect an *individual* passively or actively, active immunisation, with its more lasting properties, is the method of choice for the general population. To affect incidence and spread of a disease, immunisation must be carried out on a large scale. It is not necessary that every susceptible individual should be immunised. If the percentage protected is sufficiently high, herd immunity will prevent epidemics from spreading. Before embarking upon an extensive immunisation scheme a number of factors require consideration, *e.g.*, the prevalence and fatality of the disease, the degree of disturbance produced in those immunised, the immediate and remote success of the method and the cost involved.

In a complete immunisation scheme susceptibles would be detected, immunised with a suitable antigen, and retested for immunity at varying periods afterwards. The ideal antigen should produce immunity in a few injections and without unpleasant reactions. In no immunisation scheme are all these requirements met. Sometimes a test for susceptibility is not available, and of those available none is infallible. No antigen is completely satisfactory : some have poor immunising power; some require to be injected several times; and still others cause unpleasant reactions. There is another variable factor, viz., the *response* of the subject to immunisation. Some do not respond at all to antigenic stimuli; others react so rapidly that immunity is produced by a single small injection. Despite these difficulties artificial immunisation has now an important place in preventive medicine and against some diseases, *e.g.*, diphtheria, is a highly efficient measure.

SUMMARY OF CHAPTER IX

I. SPREAD OF INFECTIOUS DISEASES

A. *Primary Factors.*

1. Prevalence and virulence of organism (reservoirs of infection).
2. Herd immunity.

B. *Secondary Factors.*

Hygiene.
Sanitation.
Overcrowding.

Geographical influences : weather, seasons, etc.
Density of population.
Movements of population.

Fluctuations in Prevalence :

General trend.
Periodic cycles.
Seasonal prevalences.

Sporadic cases.
Endemics.
Epidemics.
Pandemics.

In epidemics—individuals affected :—

(*a*) Overt cases.
(*b*) Missed and abortive cases.
(*c*) " Submerged " cases: Latent infections. Carriers (carrier epidemics).

II. CONTROL OF INFECTIOUS DISEASES

Notification, isolation, disinfection, quarantine, immunisation, general hygienic measures for the prevention of the transmission of infectious diseases.

CHAPTER X

GENERAL MANAGEMENT OF INFECTIOUS DISEASES

IN fever hospitals patients are isolated in "units." Each unit may contain one patient or a number suffering from the same disease. Such units are isolated from each other—

A. To prevent direct transmission of infection :
  (i) By structural separation.
  (ii) By spatial separation.

B. To prevent indirect transmission of infection :
  By nursing separation—the "aseptic" technique of fever nursing.

Structural Separation.—Structural separation involves the use of wards of various types :—

(i) *The Open Ward* is a separate structure housing a number of patients suffering from the same disease. All the patients in the ward, numbering from two to thirty, constitute one infectious unit.

(ii) *The Chamber or Cell Ward* is a composite ward. It is divided into a number of separate cells by glass partitions which reach from floor to ceiling. Each cell is separately ventilated, accommodates one patient and constitutes a separate infectious unit. From the point of view of infection, it is best looked upon as a series of glass boxes grouped into a ward for convenience of nursing. In adjacent cells different diseases may be treated.

(iii) *Cubicle Wards* resemble chambers, but the partitions between beds do not reach the ceiling. They therefore have common ventilation, which, for certain infections, is undesirable.

(iv) *Separation Wards* are small side wards opening off an open ward, and rarely provide adequate isolation.

Spatial Separation.—The spacing of units and patients from one to another is an important feature of hospitals for infectious diseases. Wards are usually constructed at some distance

from each other, so that the hospital has a "horizontal" lay-out in contrast to the vertical type of building consisting of several storeys of wards. Especially in open wards spatial separation or *bed-spacing* is an important measure of control, designed to avoid overcrowding and to diminish the possibility of droplet infection from one patient to another. The standard adopted for fever hospitals is 12 ft. between bed centres.

Nursing Separation.—The "*aseptic*" *technique of fever nursing* is carried out in passing from one infectious unit to another, *e.g.*, in passing from one open ward to another, or from one cell to another. The principle of the method is that the patient, his clothing, bedding, towels, utensils, etc., and anything he touches or which touches him must be treated as infectious. No object may be in common use between two infectious units. After use by the patient, disinfection of the articles must be carried out. An attendant who touches the patient or anything belonging to him becomes "infected" and must "clean" herself before leaving the unit. The procedure adopted is for the attendant to don a gown on entering the unit, remove it when she has attended the patient, and scrub her hands with soap and hot water before leaving. In special circumstances, *e.g.*, in dealing with puerperal women and premature infants, masks should be worn, but efficient masks and masking are difficult to ensure. Caps or coifs are sometimes used and gloves are necessary in dealing with cases of venereal disease. It must be emphasised that the most important measure is thorough scrubbing of the hands.

Inside units of more than one patient, *e.g.*, in open wards, the rules of aseptic technique do not apply in passing from one patient to another. Occasionally, however, a patient in an open ward is suspected to be suffering from another infection, and immediately it becomes necessary for a nursing *barrier* to be established. It is continued until the doubt is dispelled or the patient removed from the ward. When a patient is put on "barrier-nursing" the method of nursing separation is applied although the patient is in an open ward. He is kept in bed; other patients in the ward are not allowed to approach the bed; separate utensils are provided; and a gown and washing utensils are placed near the bed so that the nurse can carry out the aseptic nursing technique when attending the patient.

Bed Isolation Wards are used when cubicle or cell accommodation is inadequate. They consist of open wards in which various diseases can be nursed together. Adequate bed-spacing is arranged to avoid droplet infection, and nursing

separation is applied to each patient to avoid indirect transmission of infection. The success of bed isolation wards depends upon the efficiency of the aseptic technique carried out by the nursing staff. If properly done all diseases can be nursed side by side, except smallpox and early cases of measles and chickenpox. With the increasing use of chamber wards (with structural separation between patients) bed isolation wards are less frequently used.

The main types of wards and their characteristics are summarised in Table VI.

The control of intercurrent infections in hospital is described in Chapter XXXVII.

Isolation in the Home.—Whenever patients are nursed at home the general principles laid down for hospital management should be applied as far as possible. The patient should be isolated in a separate, well-ventilated and warmed room, preferably at the top of the house. Aerial connection between the sick room and the rest of the house should be broken as much as possible by hanging outside the door a sheet constantly moistened with a disinfecting fluid. Probably the main virtue of the disinfectant is that it reminds occupants of the presence of infection and the necessity for care. Separate utensils should be set aside and disinfected or boiled after use. Nothing should pass out of the room unless disinfected. Dressings, poultices, rags, etc., should be burnt after use, so that it is a convenience to have an open fire in the room. The nurse or attendant should carry out the rules of the aseptic technique of nursing on entering and leaving the room. Visiting should be either prohibited or restricted to parents, who should adopt the same precautions. Unless facilities exist for these measures, it is better to send the patient to hospital.

Medical and Nursing Treatment of the Patient.—For the treatment of the patient two important measures are rest and the administration of the specific antiserum—if an efficient one is available. Drugs, with a few notable exceptions, play a minor part. Sulphonamide, used in the treatment of hæmolytic streptococcal and other bacterial infections, is considered below; organic arsenicals are specific for syphilis and Vincent's disease; dextrose (glucose) is of value in all toxæmias; and morphia, or some less potent sedative, is occasionally used to secure rest in the more severe cases.

Rest.—In some diseases, *e.g.*, diphtheria, typhoid fever, lobar pneumonia and all severe toxæmias, it is vital to keep the patient *absolutely* at rest. If the illness threatens to be so severe or prolonged as to tax the patient's reserves (particularly

TABLE VI

TYPES OF WARDS

Type of Ward	Separation of Individual Patients			Type of Case	No. of Patients in Each Infectious Unit
	Spatial	Nursing	Structural		
OPEN . . .	+	0	0	ONE DISEASE ONLY.	WHOLE WARD.
BED ISOLATION .	+	+	0	ALL DISEASES EXCEPT SMALLPOX, CHICKEN-POX AND MEASLES.	ONE.
CHAMBER . .	+	+	+	ALL DISEASES.	ONE.

the reserve power of the heart) proper rest may make the difference between death and recovery. *Absolute rest* implies the prohibition of all *voluntary* muscular movements, and the nursing of the patient in such a manner that all *involuntary* muscular activities, such as the action of the heart and digestive apparatus, are reduced to a minimum. The position which entails the least effort is the dorsal decubitus: the patient lies flat on his back without pillows. If this causes discomfort it may be modified, as discomfort results in restlessness and sleeplessness, both of which are inimical to absolute rest. The patient should be washed and fed. The effort of normal defæcation should be minimised by the use of simple enemata, purgatives being avoided at this stage. The patient should be lifted on to the bed-pan. Movements, such as changing the patient's position in bed, should be carried out by nurses.

When convalescence begins, increasing liberty should be allowed, but the transition to greater activity should be *gradual*. At first pillows should be given; then the patient should be allowed to sit up in bed, and wash and feed himself; later he should be permitted to get out of bed, to lie on a couch at first, then to sit in a chair, and lastly to walk about.

In most of the infectious diseases death or permanent disability results from complications. It is therefore important in the medical and nursing care of patients to watch closely for complications so that early treatment can be instituted.

In the milder diseases the restrictions on the activity of the patient are less, simple confinement to bed for a few days being enough for most cases.

The Ward.—A well-ventilated but warm room or ward should be provided. Fresh air is valuable, not only for its effect on the patient but also because it prevents the spread of infection. The temperature of the ward should be maintained at 60° to 65° F. Warmth increases the resisting power of the individual. If the type of heating results in excessive dryness of the air, automatic humidifiers may be installed.

Drugs.—Antipyretic drugs have little place in the treatment of infectious diseases. If it is necessary to reduce the temperature because of nervous symptoms, sleeplessness, or the existence of hyperpyrexia, physical measures, such as sponging, baths, packs or an ice-bag to the head, are preferable. The value of stimulants, such as coramine and strychnine, is also questionable. A heart failing from toxæmia, if it responds to stimulants at all, seldom does so for a sufficient time to carry the patient over the period of danger, and the stimulation has the disadvantage that it diminishes what reserve energy remains.

THE SULPHONAMIDE GROUP OF DRUGS

A group of drugs, derived from azo dyes with an attached mordant, has recently been discovered to have considerable value in the treatment of bacterial infections. The most important are :—

1. *Sulphanilamide* (para-amino-benzene-sulphonamide), *e.g.*, "Prontosil."
2. *Benzyl-sulphanilamide* (benzyl-amino-benzene-sulphonamide), *e.g.*, "Proseptasine."
3. *Sulphapyridine* (2-sulphanilyl-aminopyridine), *e.g.*, "M & B 693."

Their mode of action is uncertain, but there is evidence that they exert a *bacteriostatic* (growth-*limiting*) action on organisms. They are most effective when antibodies to the organism are present in the blood. They retard growth, preventing infection from advancing too rapidly, thereby giving the normal defence mechanism time to overcome the disease. If treatment is withdrawn too soon, there is a liability for relapses to occur, so that it is necessary to continue the drug for some days after the pyrexia subsides. It is doubtful if these drugs have any bactericidal (*killing*) action. They are of particular value in hæmolytic streptococcal infections such as puerperal sepsis, erysipelas and streptococcal meningitis, although in scarlet fever and streptococcal sore throat their value is less certain. They have been used with varying success in many other bacterial diseases, *e.g.*, meningococcal, pneumococcal, gonococcal, *B. coli* and *B. welchii* infections. They have no certain action in viral diseases, but may be used for complications due to secondary invaders such as hæmolytic streptococci. Benzyl-sulphanilamide is of little value in meningococcal infections as it does not reach the cerebrospinal fluid. Sulphapyridine has been most extensively used in pneumococcal infections.

All three are readily absorbed from the alimentary canal, and the maximum concentration in the blood is reached in two hours. They are therefore best given by mouth. Sulphanilamide is only feebly soluble and an adequate dose cannot be given by injection; sulphapyridine is insoluble, but a soluble sodium salt is available. If a soluble product is required, this or other members of the group may be used. The early successes of Colebrook and his co-workers (1936, 1937) were obtained with combined intramuscular and oral administration of "red prontosil," but this product has now been

replaced. These drugs are rapidly excreted by the kidneys; in five hours the concentration in the blood is diminished by a half, and complete excretion occurs in twenty-four hours, unless the kidneys are diseased.

The following remarks on the dosage of sulphanilamide are based upon the work of Long, Bliss & Feinstone (1939):—

The drug must be administered four-hourly during the twenty-four hours in order to maintain a constant level in the blood. The dosage varies according to body-weight and should be adjusted so that the level of the drug in the blood is 10 to 15 mgm. per 100 c.c. in severe infections and 5 to 10 mgm. per 100 c.c. in moderately severe and mild infections. The following scheme of dosage generally ensures these levels, although it may be desirable in certain cases to check the amounts by blood estimations:—

	Adults	**Children**
	Gm.	Gm.
1. **For Severe Infections—**		
Initial dose . . .	4·0 to 4·5	1·5 to 3·0
Subsequent four-hourly dose, day and night	0·75 ,, 1·0	0·25 ,, 0·5
2. **For Moderately Severe and Mild Infections—**		
Four-hourly dose . .	0·75 ,, 1·0	0·25 ,, 0·5

(Tablets are usually made up to contain 0·5 gram (gm.), *i.e.*, 7½ grains, of the drug.)

The common *by-effects* of these drugs are seldom sufficiently severe to justify withdrawing them from cases in which they are indicated, although occasionally serious toxic symptoms occur which, in rare instances, have resulted in death.

To avoid sulphæmoglobinæmia (one of the symptoms of which is cyanosis) saline cathartics, such as magnesium sulphate, should not be administered, either internally or as an external dressing. Eggs and onions should also be avoided. Alcohol is contraindicated as it increases the liability to toxic cerebral manifestations.

Sodium bicarbonate should always be administered with these drugs to prevent acidosis. Patients should, for preference,

BY-EFFECTS OF SULPHANILAMIDE

Frequency	Toxic Manifestations	Remarks
(*a*) Common	Cyanosis	Sometimes due to methæmoglobinæmia or sulphæmoglobinæmia. Rarely severe enough to justify withdrawing the drug.
	Anorexia, nausea	Rarely severe enough to justify withdrawing the drug.
	Mild hæmolytic anæmia (see (*c*) below)	Not dangerous: continue drug but watch the patient carefully.
	Slight granulo-cytopenia (see (*c*) below)	Watch the blood count carefully.
(*b*) Not common . . .	Drug fever (simple pyrexia)	Important warning sign; stop the drug.
	Acidosis	Can be prevented by the routine use of sodium bicarbonate.
	Rashes (usually morbilliform)	Best to stop the drug.
	Vomiting	May be necessary to use parenteral route.
	Dizziness and cerebral toxic symptoms	Best to stop the drug.
(*c*) Rare	Acute hæmolytic anæmia	Stop the drug (may be given with multiple transfusions).
	Agranulocytosis or progressive granulo-cytopenia.	Stop the drug.
	Jaundice (without anæmia)	Stop the drug.
	Renal irritation	Stop the drug.

be in hospital during treatment and their temperatures taken regularly. Daily blood examination (hæmoglobin and white cell count) should be carried out whenever practicable. Fluids should not be forced as they tend to wash out sulphanilamide (excreted in the urine) and lower the blood level. For this reason, water in large quantities is the antidote for toxic manifestations.

Backhouse (1939) reports on the frequency of hæmaturia following the administration of sulphapyridine. The cause is mechanical, not toxic, due to irritation from crystals of the acetyl component, which is relatively insoluble. Its occurrence necessitates the administration of ample fluids.

SUMMARY OF CHAPTER X

Isolation of infectious units from each other :—

(i) Structural separation.
(ii) Spatial separation.
(iii) Aseptic technique of fever nursing.

Types of wards : Open, chamber, cubicle.
Medical and Nursing Treatment.
Sulphonamide Group of Drugs.

CHAPTER XI

DIET IN INFECTIOUS DISEASES

THERE is no convincing evidence that diet has any direct effect upon an infection, but a suitable diet, by maintaining the physiological activities of the body at their best level, permits the elaborate protective mechanism to operate at its greatest efficiency. The increased metabolic activity which accompanies pyrexial states results in increased destruction of tissues, and accumulation of waste products. Toxæmia, which occurs in every acute infection to a varying degree, impairs the activities of all organs including the detoxifying and excretory organs like the liver, kidneys, bowels, etc. Thus the very organs which, during fevers, should be more active than in normal states, are themselves partially poisoned. The digestive and assimilative apparatus is impaired as part of the general disturbance and the glandular secretions are diminished. Moreover, anorexia and nausea are common symptoms. These factors influence the type of diet which may be given.

The fundamental requirements are the same as in health : carbohydrates, proteins, fats, salts, water and vitamins. The construction of a suitable diet is but the adaptation of the normal to the changed metabolic circumstances. A rational diet should be acceptable to the dulled palate of the patient, make as little demand as possible on the digestive, assimilative and excretory organs, supply energy for the increased metabolic activities, replace the excess tissue loss, maintain the biochemical reactions of the body, and assist in the elimination of waste products. In practice these requirements can seldom be met because of the limitations imposed by the patient's appetite, powers of digestion and of assimilation. Actually the patient may be unable to tolerate a diet of sufficient energy (caloric value) for normal requirements, although, because of his fever, his caloric requirements may be 100 to 200 per cent. above normal. There is thus a danger of semi-starvation in the pyrexial stage of the disease.

Diets in infectious disease are therefore usually constructed in three stages :—

1. *The Onset Diet,* intended to be of short duration and suitable for the initial stages of fever. It is based on the principles of relative intestinal rest by the prescription of easily digested foods, but the caloric value is low.
2. *The Continuation Diet,* in which the caloric value is increased, but the principle of relative rest of the digestive apparatus is maintained. It is continued for as long as the fever persists. In diseases with continued pyrexia, *e.g.*, in typhoid fever, this state is of the utmost dietetic importance.
3. *The Recovery Diet* is intended to make up the losses of the two previous stages, and is constructed to contain a high caloric and high protein content.

In most of the common infectious diseases the initial pyrexia is of short duration, seldom lasting for more than a few days. In these diseases transition through the three stages takes place rapidly. In the mild diseases such as rubella and chickenpox, and even in the mildest forms of scarlet fever and diphtheria, the disturbance to the patient is so slight that the initial stage can frequently be omitted. Diets of this type are suitable for almost all the acute infections and may be called the *general fever diet.*

Special diets are indicated in certain diseases, *e.g.*, in enteric fever, dysentery and infectious enteritis ; in certain cases of whooping-cough ; for the renal disorders complicating scarlet fever ; and when the state of the patient is such that normal methods of feeding cannot be employed.

General Fever Diet.—The onset diet is usually a fluid or soft one. It consists principally of variations of the following articles of diet : water, milk, sugar, eggs, cereals and fruit juices.

Water constitutes a high proportion of the body-weight and all the essential biochemical reactions take place in the fluid. During fever water is necessary for allaying thirst, making up the excessive losses, flushing the excretory organs and assisting in the heat regulation of the body. The maximum amount which the patient will tolerate is therefore indicated, but forcing fluids is rarely desirable. To provide variety, and render it more palatable, water may be flavoured in various ways (lemonade, orangeade, barley water, "aerated" waters), or given in the form of broths, clear soups or beverages (tea, coffee, chocolate, cocoa). These alternatives, particularly those made up with milk and sugar or fresh fruit juices, contain

other useful constituents, but their essential value lies in their water content. All the rest of the articles in the onset diet are liquid or soft foods, which, although containing water, are given primarily for their food content. Fluids may be taken cold, iced or at room temperature. There appears to be some therapeutic value in hot drinks ; and iced drinks are particularly acceptable to patients with pyrexia.

Milk.—Since milk contains all the essential ingredients of a diet, it is a complete food in itself ; and as it is readily digested, it occupies first place as an article of diet in fevers. It loses vitamins during heating and pasteurisation, but this deficiency can readily be made up. To avoid monotony milk modifications may be used. Malted milk, milk flavoured with tea, coffee, chocolate or cocoa, ovaltine, milk shakes, buttermilk, junket, ice-cream, custards, are examples. Some adults, and a few children, dislike milk. For the adult with a taste for alcohol, milk punch, containing whisky or sherry, may increase palatability. In some patients with alimentary disorders, and particularly in children, whole milk is not well tolerated. Modifications may be made by the removal of certain constituents, as in evaporated milk, sweetened condensed milk, skimmed milk, whey, and homogenised milk.

Sugars.—The chief function of carbohydrates is to supply energy for the body. They are readily digested and assimilated, and most of them, particularly the pure sugars, are pleasant to take. They are therefore valuable as fuel for the increased metabolism accompanying the acute fevers. It is essential that important organs, such as the heart, should not lack adequate food during their enforced hyperactivity under toxic conditions. Glucose has therefore attained a therapeutic importance and is administered not only in food but also intravenously and per rectum. It is likely that glucose has some value, other than its food value, in toxic states. For a pure sugar ingredient of the diet ordinary cane or beet sugar is more easily obtainable. Syrup and honey are pleasant alternatives. For children (and not for them alone) boiled sweets, barley sugar, and chocolate are pleasant forms of sucrose.

Cereal Foods consist largely of carbohydrates (mostly starches), but with smaller amounts of other constituents. Bread, toast, biscuits and cake are the most important varieties. Cereal gruels, made from wheat, rice, barley and oatmeal, have had a long usage, both in the home and in hospitals, as an invalid food.

Fruit Juices are most suitable as constituents of the fever

diet. They contain carbohydrates and vitamins. Their acid taste is pleasant and refreshing to the mouth. Some fruit juices contain acids which leave an alkaline ash, and those containing citric acid, such as oranges, lemons, grape-fruit and tomatoes, are particularly useful. Purées of apples, prunes, peaches and pears may be employed as adjuncts to the soft diet.

Eggs are a useful article of diet because they supply protein and fat in a palatable and readily digestible form, and contain vitamins. When fat is not tolerated, the white only may be employed. Added to fluids, such as lemonade and milk, egg white or whole egg reinforces the purely liquid diet. Soft-boiled, scrambled and poached eggs, and omelettes are introduced a little later, when the fluid diet gives place to the soft diet.

Proteins and fats are present in some of the foods supplied at this stage, but articles of diet containing them in relatively high proportions are not suitable. Meats, green vegetables and foods difficult of digestion because of their mode of preparation are contraindicated. Fried, baked, roasted and grilled foods are unsuitable. In the soft diet mashed potatoes are useful for their carbohydrate content and purées of legumes, such as peas, beans and lentils, for their nitrogenous constituents.

Considerable importance has been attributed to the action of vitamins and the necessity for a high vitamin content in the diet of a fever patient. In normal children there is no convincing evidence that an excess above normal requirements has any prophylactic or therapeutic effect in infectious diseases. The only consideration in constructing a suitable fever diet is to ensure the supply of the normal amounts. If, however, there is evidence that a child is suffering from an overt deficiency of vitamin A or D, resistance to infection is reduced and the vitamin requirements are much higher. There is a loss of vitamin C in fevers, and it has been suggested that vitamins B and C have a therapeutic value, but this is not yet proved.

Continuation Diet.—As soon as possible, and seldom longer than twenty-four to forty-eight hours after the onset, the purely fluid diet should be replaced by a soft diet, which should be gradually increased until the patient can take the full restoration diet. In introducing flesh foods, it is better to start off with fish, fowl, rabbit and tripe, and to leave those more difficult to digest, such as pork, beef, veal and mutton, until later.

In all stages of the fever, and particularly at the beginning, small feeds at frequent intervals should be prescribed. Since

the requirements of the body are not fully met in the first two stages, the return to the normal diet should take place as soon as possible. The appetite of the patient is the best guide to the quantity of food he will tolerate, the intervals at which feeds can be taken and the time for transition from one stage of the diet to the next. Monotony should be avoided. Within the limits prescribed by the stage of the disease, the tastes and dietetic habits of the patient are the best guide to the selection of suitable constituents.

SUMMARY OF CHAPTER XI

General fever diet :—

(i) Onset diet.
(ii) Continuation diet.
(iii) Restoration diet.

CHAPTER XII

HÆMOLYTIC STREPTOCOCCAL FEVERS

I. IN GENERAL. II. SCARLET FEVER AND INFECTIOUS SORE THROAT. III. ERYSIPELAS. IV. PUERPERAL SEPSIS

I. IN GENERAL

DEFINITION.—Hæmolytic streptococcal fevers comprise a group of widely differing diseases caused by the same organism—the *hæmolytic streptococcus*.

Bacteriology.—Many varieties of streptococci exist, not all of which are human pathogens. Those responsible for the hæmolytic streptococcal fevers produce, when grown upon a solid medium containing blood, a zone of complete hæmolysis (a pale colourless halo—β-hæmolysis) around the colonies. Classification is difficult; two methods are commonly used :—

(i) Lancefield divides them into *groups, e.g.*, A to M, by a *precipitin* test, using *soluble products* of the organism. Most human pathogens belong to Group A.

(ii) Griffith divides them into *types* by an *agglutination* test, carried out on the *intact organism* with a type specific serum. Some twenty-six types have been described, certain of which are commonly associated with the hæmolytic streptococcal fevers.

It is important to realise, however, that none of these conditions is due to one type only, *e.g.*, scarlet fever may in one patient be due to type 1, in another to type 2, in a third to type 4. On the other hand, two clinically distinct diseases such as scarlet fever and puerperal septicæmia may be due to the same type of hæmolytic streptococcus. The factors which determine which clinical syndrome results are the following :—

1. The general and local tissue resistance of the patient. Special mention should here be made of the resistance of the skin as it plays an important part in determining the appearance of the typical toxigenic rash (*vide infra*).
2. The velocity of infection (*vide* Chapter II, p. 9).

3. The mode of entry of the organism, whether inhaled, ingested or inoculated ; and, if inoculated, into which part of the body.
4. The properties of the particular strain of hæmolytic streptococcus. Of these properties two are specially important :—
    (*a*) The *invasive power* of the strain. Some strains are readily localised by the resistance of the tissues ; others invade readily, spreading either along tissue planes or entering the lymphatic and blood streams.
    (*b*) The capacity of the strain to produce an *exotoxin*. Various toxins have been described, such as hæmolysins, fibrolysins, etc., but in this group the *erythogenic*, *i.e.*, rash-producing, toxin is the most obvious. The power to produce erythrogenic toxin varies considerably with the strain. Those which are feeble in this respect are incapable of causing a rash, however severe the streptococcal infection may be.
    (*c*) The other factor which determines whether a rash appears is the *susceptibility* or the *resistance of the skin* to the erythrogenic toxin. This, in turn, depends upon the amount of antitoxin circulating in the blood and fixed in the tissues.

    The intradermal test, *i.e.*, the *Dick Test*, is used to determine the resistance or susceptibility of the skin. Since a rash due to this toxin is a feature of clinical scarlet fever, the Dick test is employed to determine susceptibility or immunity to this disease. The commonest *rash* produced by the erythrogenic toxin is a punctate erythema — the typical rash of scarlet fever. Hence, every hæmolytic streptococcal infection associated with a punctate erythema is to be considered as scarlet fever of one or other type (*vide infra*).

VARIETIES OF HÆMOLYTIC STREPTOCOCCAL INFECTIONS

The following classification of hæmolytic streptococcal infections is based firstly upon the invasive power of the

organism, secondly upon the site of entry, and thirdly upon the presence of a rash. This order is chosen because it is the order of importance of the features of the disease. A rash is never a dangerous sign, although it may be alarming because it is so obvious; on the other hand, an infection with an invasive strain may be rapidly fatal although the clinical signs may not be striking.

1. **Diseases due to Local Invasion only.**—If the hæmolytic streptococcus shows little invasive power, the infection is localised to the portal of entry, and sets up a local septic lesion. Depending upon the site of entry, various clinical pictures are produced :—

(*a*) *Inoculation.*—The organism may enter through some macroscopic or microscopic breach of the skin or mucous membrane. In this way are produced septic cuts and abrasions, septic surgical wounds, septic burns, whitlows, impetigo and septic perineal tears. Most of these are simple septic lesions not usually classed as infectious diseases; but they can produce a severe and fatal disease, such as puerperal septicæmia, if transmitted under suitable conditions to a susceptible subject. Realisation of this important fact is responsible for the now generally accepted rule of obstetric practice that midwives suffering from such septic lesions must not attend women in labour. A special variety of local streptococcal infection of the skin is *erysipelas*.

(*b*) *Inhalation.*—When hæmolytic streptococci are inhaled, they may set up local lesions in the respiratory tract. Usually the upper part of the tract is involved, although the whole may be affected. The most common conditions are rhinitis, tonsillitis and pharyngitis; less common are bronchitis and bronchopneumonia, which may be the result of spread from above—due, in fact, to the invasiveness of the organism. In all these conditions the droplets expelled contain hæmolytic streptococci and are therefore infectious. If inhaled by a second person, they may set up a similar streptococcal respiratory infection; if the droplets are expelled on to a damaged skin or mucous membrane—such as on to a perineal tear—they may produce one of the other types of streptococcal disease. For this reason midwives with upper respiratory tract infections should not

attend women in labour. (It should be noted that some healthy people carry hæmolytic streptococci in the respiratory tract and for the same reason they are dangerous.)

(c) *Ingestion.*—Occasionally hæmolytic streptococcal infections occur from the ingestion of infected milk or other food.

Whenever a streptococcal infection occurs, whether as the result of inhalation, ingestion or inoculation, toxins are produced at the site of the local lesion and are absorbed into the circulation. If the toxin is erythrogenic and if the patient's skin is susceptible (*i.e.*, if he is a Dick reactor), a punctate erythema appears and the patient suffers from *scarlet fever.* If the local lesion is in the fauces, scarlet fever is of *ordinary* type ; if the local lesion is an infected wound or burn, the condition is *surgical* scarlet fever ; if the local infection is of the perineum or genital tract following childbirth, the condition is *puerperal* scarlet fever. Not infrequently, in surgical and puerperal scarlet fever, the local lesion is insignificant or is overlooked.

2. **Diseases due to Spread beyond the Local Lesion.**—The invasive property of the hæmolytic streptococcus is independent of the erythrogenic factor. When the organism spreads from the local lesion it may affect adjacent or contiguous local structures, or it may spread through tissue planes, or it may enter the lymphatic stream or the blood stream.

From the fauces infection may spread to the local lymphatic glands, causing adenitis or abscess, or along the Eustachian tube to the middle ear, causing otitis media, whence it may spread to the mastoid, lateral sinus, meninges, brain, etc. From a local lesion of the skin, spread may take place along the connective tissue planes producing cellulitis, or along the lymphatic system causing lymphangitis and adenitis. In hæmolytic streptococcal *puerperal infections* all grades of invasive and toxic features may be observed. Apart from the local lesion already considered, infection may spread along the genital tract, producing endometritis, salpingitis, pelvic peritonitis or general peritonitis ; it may invade the pelvic cellular tissue, producing parametritis or pelvic cellulitis ; or it may infect the blood stream directly, through the lymphatic system, or through an infected venous clot, producing septicæmia or pyæmia. In addition to any one of these invasive features, there may be a scarlatiniform rash, indicating the action of the erythrogenic toxin in a Dick-positive subject.

TABLE VII—RELATIONSHIP OF THE DIFFERENT TYPES OF SCARLET FEVER TO OTHER HÆMOLYTIC STREPTOCOCCAL INFECTIONS IN DICK-POSITIVE PATIENTS.

These are representative examples: other combinations are possible. Although the local lesion is marked as + in every case, sometimes it is so slight as to be overlooked.

In Dick-negative subjects all types of scarlet fever are ruled out.

Portal of Entry	Hæmolytic Streptococcus				Result in Dick-*Positive* Patients.
	Invasiveness			Erythrogenic Toxic Production	
	Local Lesion Only	Local Spread	General Spread		
Fauces (by inhalation or ingestion)	+	0	0	0	Acute tonsillitis (or tonsillo-pharyngitis or rhino-pharyngitis).
	+	0	0	+	Scarlet fever.
	+	+	0	+	Scarlet fever with complications, *e.g.*, otitis media, adenitis.
	+	+	+	+	Scarlet fever with septicæmia.
Wound or burn (by inoculation)	+	0	0	0	Septic wound or burn.
	+	0	0	+	Surgical scarlet fever.
Female genital tract (by inoculation)	+	0	0	0	Infected perineal or cervical tear or infected placental site.
	+	0	0	+	Puerperal scarlet fever.
	+	+	0	0	Endometritis, salpingitis, cellulitis, pelvic or general peritonitis.
	+	+	+	0	Puerperal septicæmia.
	+	+	+	+	Puerperal septicæmia and puerperal scarlet fever.

It will thus be obvious that the *rash* in scarlet fever, upon which such importance was placed in the past, is relatively unimportant ; and the rigid separation of conditions associated with a rash from those without is artificial and confusing. In Table VII the position in Dick-positive subjects is summarised. In Dick-negative subjects erythrogenic toxin production is of no significance, as the patients are not susceptible to the toxin.

Nevertheless, although there is this overlapping of the hæmolytic streptococcal fevers, in the majority of cases they breed true, *i.e.*, one case of scarlet fever tends to give rise to other cases of the same disease ; erysipelas, impetigo, tonsillitis, etc., behave in the same way. This may, in part, be due to the type of streptococcus and in part to "tropism," *i.e.*, the development by the organism of an affinity for particular tissues.

II. SCARLET FEVER

Definition.—A local hæmolytic streptococcal infection with an accompanying toxæmia. The local manifestations occur at the portal of entry, which is usually the fauces or pharynx. The onset is sudden with headache, vomiting, sore throat, pyrexia and a punctate erythema which appears on the second day. Complications, when they occur, usually involve the cervical glands, middle ear and the kidneys.

1. **Bacteriology.**—The hæmolytic streptococci responsible for scarlet fever belong to Lancefield's Group A, and include a number of the Griffiths types, *e.g.*, in London 50 per cent. of cases of scarlet fever are due to types 1 to 4 (Allison, 1938).

The organism can be recovered in large numbers from the local lesion. It is also present in the discharges. In the ordinary case of scarlet fever a swab from the throat or nose, spread on to a blood agar plate and incubated at 37° C., shows the typical colonies with a zone of hæmolysis in twenty-four hours. Because of the many types of hæmolytic streptococci, the frequency with which they are found in normal throats and the difficulty of classifying them, swabbing of the throat and nose is not carried out as a routine in scarlet fever. It is, however, used as an aid in the diagnosis of difficult cases. Swabbing and typing are also carried out to trace the *source* and *paths* of infection in outbreaks of the disease. The organisms are most profuse and most easily detected in the early stages, and persist for a variable period ; in a high percentage of cases they can still be recovered three or four

weeks after the onset. However, because of the difficulty of typing the organism, release cultures for freedom from infection are rarely used as a routine.

2. **Immunology.**—Almost all infants under one year are immune to scarlet fever. When the infantile immunity wanes most children are left susceptible. As they grow older an increasing number acquire immunity from latent infections ; but even among adults immunity is not general. The disease is, however, most common in children between one and ten years (80 per cent.).

Dick Test.—Susceptibility or immunity to scarlet fever is determined by the Dick Test. The material used is the exotoxin produced by the hæmolytic streptococcus when grown in a fluid medium. The amount used is a *skin test dose.* This quantity cannot be accurately measured in the laboratory and its estimation is usually carried out on susceptible human subjects. The toxin is diluted so that 0·2 c.c. contains one skin test dose, and this quantity is injected intradermally when performing the test. A positive reaction, indicating susceptibility, appears in eight to twelve hours and consists of a patch of uniform erythema. It disappears in twenty-four to seventy-two hours, rarely leaving staining. Positive reactions vary considerably in their size and intensity, depending upon the degree of susceptibility of the subject. If no reaction follows the injection, the Dick test is negative and the subject immune. Faint reactions of less than 10 mm. diameter are to be considered negative. It should be remembered that a negative reaction strictly means immunity to the toxin, so that while some Dick-negative subjects are immune, not only to the toxin but also to the organism itself, a number are immune only to the toxin ; in these hæmolytic streptococcal infection can occur, but no rash follows. Those immune to the toxin, *i.e.*, Dick-negative reaction, have probably had the opportunity of developing some immunity to the organism itself ; but the Dick test is no measure of such antibacterial immunity.

False or pseudo reactions are rare in the Dick test. When they occur they appear a little later than the true positive (twenty-four to forty-eight hours) and disappear within three days. Pseudo reactions are detected by using a control injection consisting of autoclaved, *i.e.*, inactivated, toxin. Thus if a reaction appears around the control injection equal in intensity to that around the toxin it is obviously false.

The main differences between Schick and Dick tests are tabulated on p. 98.

TABLE VIII

Comparison of Schick and Dick Tests

	MATERIAL	USE	POSITIVE REACTION			FALSE REACTION
			Time of Maximum Intensity	Time of Fading	Residual Pigmentation and Desquamation	
SCHICK TEST	0·2 c.c. diluted filtrate containing $\frac{1}{50}$ M.L.D. of the exotoxin of *C. diphtheriæ*	To determine susceptibility or immunity to diphtheria	Two to four days	Seven to ten days	Not uncommon	Not uncommon
DICK TEST	0·2 c.c. diluted filtrate containing 1 "skin test dose" of the exotoxin of the hæmolytic streptococcus	To determine susceptibility or immunity to scarlet fever	Twelve to twenty-four hours	Within three days, often earlier	Absent	Rare

At the beginning of an attack of scarlet fever the Dick test is usually positive. In fourteen to twenty-one days, because of the immunity acquired during the course of the disease, the test usually becomes negative. This change-over from the positive to the negative state is evidence in a doubtful case that the subject has been suffering from scarlet fever.

It is important to realise that the Dick test is not accurate in 100 per cent. of cases. Occasionally Dick-negative subjects

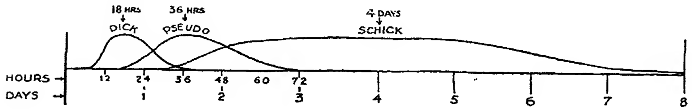


FIG. 8.—Comparison of the Time of Onset, Maximum Intensity and Duration of the Schick and Dick Tests and Pseudo Reactions.

develop the disease; not infrequently during an attack of scarlet fever the Dick test fails to change over to the negative state. On the other hand, the change over sometimes takes place very early, *e.g.*, in three or four days. Subjects who remain Dick-positive after a clinical attack of scarlet fever are more liable to relapses and second attacks, both of which occur in scarlet fever. It is generally agreed that relapses are due to reinfection, often with a different serological type of hæmolytic streptococcus.

Prevention of Scarlet Fever by Artificial Immunisation.—Artificial immunity may be induced actively or passively.

Active immunisation by the injection of scarlatinal toxin is not considered to have reached a high state of perfection yet for these reasons: it is necessary to give five injections at weekly intervals; reactions of some severity are not uncommon, particularly after the first two injections; and the duration of immunity is uncertain. As scarlet fever is a relatively mild disease, it is not considered justifiable to employ the method generally; its use is largely restricted to staffs of hospitals and to inmates of institutions such as residential schools, where the probability of exposure to the disease is higher than among the ordinary population. A preliminary Dick test should be performed to detect susceptible subjects. Immunising injection should be made subcutaneously, as less likely to produce general reaction. The initial dose should be 500 s.t.d. (skin test doses) unless the patient is strongly Dick-positive, when it should be reduced to 200 s.t.d. Thereafter increased doses may be given until 80,000 to 100,000

s.t.d. are injected as the last dose. Reactions, when they occur, may vary from slight malaise to sharp attacks of headache, vomiting, pyrexia, with a scarlatiniform rash appearing in about thirty-six to forty-eight hours. Severe reactions are uncommon. The method is fairly efficient. In 85 to 95 per cent. of cases immunity develops, as determined by a post-Dick test performed within a month of the last injection. The duration of immunity is variable—from one year upwards—but on the average protects the subject against an attack for a sufficient number of years to permit the development of a naturally acquired immunity.

To eliminate the objectionable features of the method, modified antigens, such as scarlatinal toxoid, by the same or other routes, such as the percutaneous, the nasal and oral, have been tried, but the results are not satisfactory.

Passive immunisation may be used to protect those who have been exposed to the disease. From 5 to 10 c.c. of scarlatinal antitoxin or 0·75 to 1 c.c. of protein-digested (globulin-modified) serum administered intramuscularly provides a passive immunity which cannot be depended upon to last for more than ten to fourteen days.

The **Incubation Period** of scarlet fever ranges from **two** to **four** days, with limits of one to seven days. Longer periods are recorded, but frequently imply a missed case or a carrier to whom the patient has been exposed at some intermediate stage.

CLINICAL FEATURES

The **onset** is abrupt in most cases. General symptoms such as headache, malaise, shivering, general aches or pains, a rigor occasionally, nausea, vomiting, constipation and pyrexia are associated with the predominant local manifestation, a sore throat. On the second day, *i.e.*, twenty-four to forty-eight hours after the onset, the typical rash appears. Before then it is impossible to make a diagnosis of scarlet fever, although the appearance of the fauces and tongue may suggest a hæmolytic streptococcal infection.

General symptoms, although fairly constant, vary in severity from a mild indisposition, which may be overlooked by parents, to a moderately severe disturbance. Scarlet fever has changed in type during the last century, and is at present a mild disease ; the severe attacks of bygone days are now rare.

Headache, although variable, is usually severe and frontal in distribution.

Vomiting occurs once or twice in the first twenty-four hours in many, but not in all, cases. As it is an objective manifestation, it may be the first indication of illness in a child who is unable to complain. Sometimes there is complaint of abdominal pain, and this, with the vomiting and the constipation due to toxæmia, may suggest an abdominal condition. Sometimes the abdominal pain is due to a purgative administered because the child was unwell.

Sore throat is almost constant and may be mild, moderate or severe. Dysphagia and pain referred to the one or both ears are occasional concomitants of sore throat; but every patient with pain in the ears requires otological examination. Cough and catarrhal symptoms are rare, although a little thin nasal discharge is not uncommon.

Signs of Scarlet Fever.—The main *objective* manifestations of scarlet fever are *pyrexia*, the *enanthem, i.e.*, the appearance of the throat and tongue, and the *exanthem* or rash.

Pyrexia.—Corresponding with the abrupt onset, the temperature rises suddenly in the first twenty-four hours to 100° to 103° F., reaches its maximum on the second or third day and declines to normal towards the end of the week. If scarlatinal serum is given the temperature falls quickly to normal in about twenty-four hours after the administration; but with the mild disease now prevalent the duration of pyrexia in an untreated case may be as short as four days, and the administration of serum to such cases on the second or third day does little to shorten the pyrexial period. The *pulse rate* is increased out of proportion to the rise in temperature. In children a rate below 120 is unusual.

Enanthem.—A diagnosis of scarlet fever should not be made in the absence of the typical manifestations of the disease in the fauces and mouth. The *tonsils* are enlarged and reddened —a catarrhal tonsillitis. In some cases small follicular spots of exudate are present. Occasionally the surface of the tonsils is covered by a soft whitish deposit which is readily scraped off with a spatula without causing bleeding. Only in the most severe cases does the exudate extend beyond the tonsils, and when it does it usually involves the anterior pillars of the fauces. In the septic type of the disease (*vide infra*) there may be ulceration of the mucosa beneath the deposit. The tonsillar glands (the cervical lymphatic glands draining the tonsils) are usually slightly enlarged and tender. The appearance of the *tongue* may be characteristic, but the changes are not present in every case. On the *first* day the tip and margins of the tongue are reddened, and the dorsum is coated with a white

fur ; in a few hours the swollen red papillæ project through the fur, producing an appearance which has been described as the "white strawberry" tongue. On the *second* and *third* days the fur peels off, first along the sides and tip and then from the centre, so that on the *fourth* day the tongue is clean and red

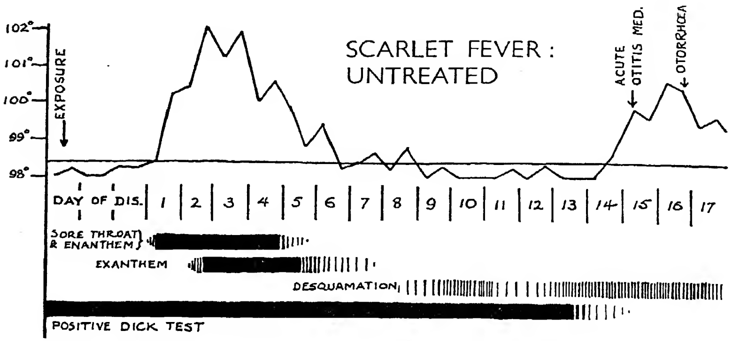


FIG. 9.—Moderate Attack of Scarlet Fever ; no Specific Treatment.

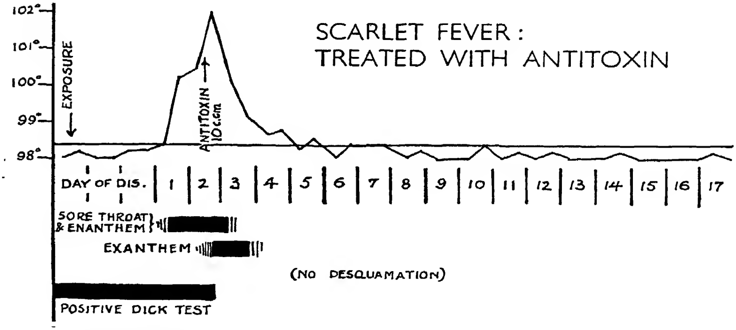


FIG. 10.—Moderate Attack of Scarlet Fever treated with Scarlatinal Antitoxin on the Second Day: rapid disappearance of initial symptoms; no subsequent desquamation.

with prominent papillæ, the so-called "red strawberry" or "raspberry" tongue. The colour of the tongue changes from a bright to a dull red before returning to its normal shade of pink. The mucosæ of the palate, pharynx, cheeks and nose exhibit an injection which varies from a slight redness to considerable congestion.

In the ordinary case of scarlet fever the palate shows a

stippled, or *punctate*, redness; and the anterior pillars of the fauces, the free margin of the soft palate and the uvula are uniformly congested and slightly swollen, producing an *arch of erythema* around the fauces. Occasionally a few petechial hæmorrhages are seen in the vault of the palate.

These changes in the upper respiratory tract are characteristic not of scarlet fever alone but of an infection with hæmolytic streptococci.

Exanthem.—The typical *rash* of scarlet fever usually appears on the second day, occasionally on the first, rarely on the third. It consists of a *punctate erythema*—an underlying flush of the skin with superimposed, closely set, minute spots of more intense redness. In the ordinary case the background varies from a light flush to a bright, but not intense, redness. In pronounced cases the background is of a vivid scarlet hue, like the colour of a boiled lobster; but such cases are rare to-day. On the face the punctiform arrangement does not occur; instead, there is at first a uniform redness, rapidly fading around the mouth and leaving a *circum-oral pallor*, in marked contrast to the flush on the cheeks and chin. Circum-oral pallor is not present in every case of scarlet fever, and in any case is not pathognomonic.

Upon the distal parts of the extremities the rash is frequently coarse and macular. The rash does not erupt simultaneously over the body. It first appears as a flush on the face and a punctate erythema on the neck and chest; rapidly involves the rest of the trunk and the proximal parts of the upper extremities; spreads to the rest of the upper extremities; and lastly appears upon the lower extremities. In about twenty-four hours, more or less, the rash becomes generalised, tending to be more intense in the warm folds such as the axilla, the bend of the elbow and the groins, and at sites of pressure such as the buttocks. The rash persists for two or three days and then gradually fades so that its total duration is from three to six days. If scarlatinal antitoxin is given, the rash fades in about twenty-four hours.

Although the rash is a hyperæmia and therefore fades on pressure, other elements, commonly present, do not fade: (i) Slight *pigmentation* at the sites of greatest intensity, persisting for a short time after the rash has faded and thus of value in the diagnosis of late cases. The best sites for observing it are the flexures of the elbows, where it forms transverse lines in the creases of the skin, and on the abdomen. (ii) *Punctate hæmorrhages* are usually sparse and are most commonly seen in the flexures of the elbows (Pastia's sign) and about the

shoulders. They are not of serious import (*cf.* the fatal hæmorrhagic type). (iii) Occasionally tiny papular elevations, instead of puncta, are seen, particularly on the legs. (iv) When the rash is intense, minute vesicles may appear (miliary sudamina) containing fluid at first clear but later becoming turbid. They are most common on the hands, feet and lower part of the abdomen, but may be widespread over the body.

Itching occasionally occurs in scarlet fever, but is rarely marked.

It will thus be seen that by the second or third day the disease is fully developed—general disturbance and pyrexia are at their highest, the rash is generalised and the fauces and tongue exhibit their typical features. Having reached its acme, the disease declines within the next few days. The temperature falls, the sore throat subsides, the rash fades and the general condition improves, so that by the end of the first week the patient enters the convalescent stage.

Desquamation.—At the end of the first week—sometimes before the rash has faded—the epidermis begins to flake or peel. The degree and the character of the desquamation depend to a considerable extent upon the intensity of the rash and the thickness of the epidermis. If the rash was slight and of short duration, the desquamation may be so trivial as to escape detection; if the rash was intense and prolonged, thick epidermal flakes may be cast off. On the hands and feet, where the epidermis is thick, desquamation is always more marked; and in mild cases these may be the only places where it is in evidence.

Desquamation appears and disappears in the same order as the rash. It is first seen on the face, as a fine powdering, as early as the fourth or fifth day. It next appears on the neck, trunk and proximal parts of the extremities about the seventh day or later. In these situations it usually has the characteristic pinhole appearance—small circular areas of desquamation appear with the central part denuded of epidermis, producing an appearance like a pinhole with a small collar of desquamating epidermis around it. Often the areas are much larger than a pinhole. By the end of the second week desquamation is general. The last parts to be involved are the hands (fourteenth day) and feet (twenty-first day), where the desquamation may consist in a slight roughness, definite pinholes or thick flakes; in the most extreme cases glove-like epidermal casts or moulds are shed. Sometimes the first evidence of desquamation on the fingers is a splitting of the epidermis near the free margins of the nails. In the mild

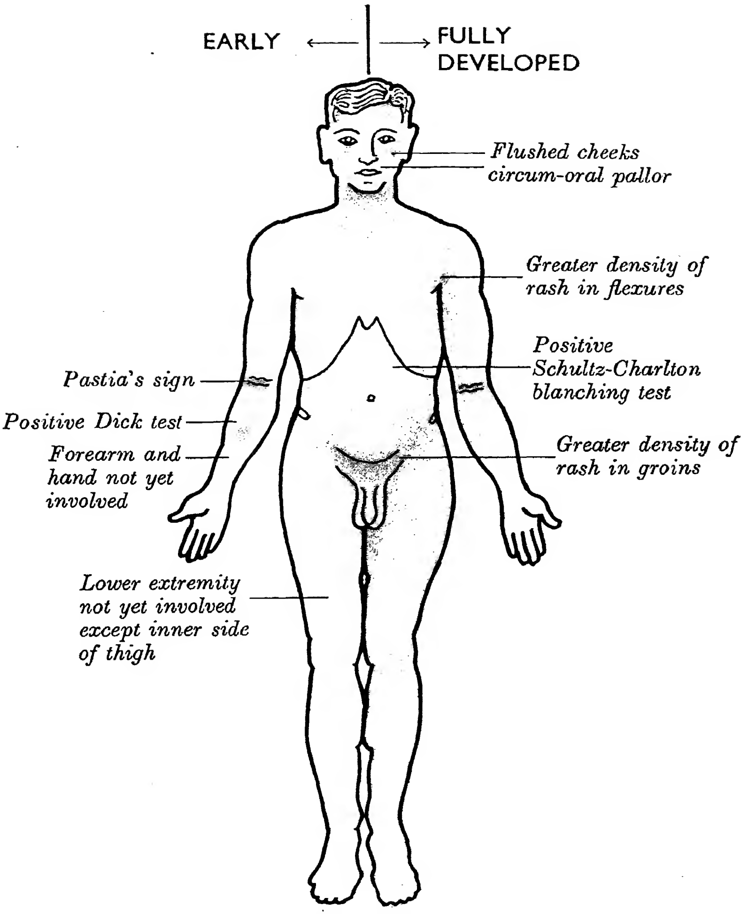


FIG. 11.—Scarlet Fever. Distribution of the exanthem—early on the right, fully developed on the left—and cutaneous tests. The punctate character of the rash on the trunk and limbs is not illustrated.

[*To face p.* 104

type of scarlet fever now prevalent, desquamation is usually slight and is complete by the end of the fourth week ; when more marked it may last for five or six weeks ; and with heavy desquamation the palms and soles may not be clear for seven weeks. Desquamation is the result of the action of scarlatinal toxin on the skin. The desquamating epidermis contains no organisms and is therefore *not infectious*. Scarlatinal antitoxin, by neutralising the toxin and aborting the rash, considerably minimises desquamation or eliminates it entirely.

Complications.—Although the complications of scarlet fever may occur at any stage of the illness, they are most common at (*a*) the beginning of the illness, whilst the ordinary manifestations of the disease are still present ; the temperature fails to decline in the usual manner and the pyrexia is explained when the complication is detected ; (*b*) the beginning of the third week, *i.e.*, about fourteen to sixteen days, when the patient is being allowed out of bed for the first time ; in such cases an apyrexial period intervenes between the initial manifestations and the complication.

The following are the most common complications :—

(i) *Cervical Adenitis.*—The lymph glands which become tender and swollen are invariably those draining the fauces and pharynx. Extreme enlargement is rare. The condition usually subsides under treatment in a few days. Sometimes the mass of glands breaks down, resulting in *suppurative adenitis*, requiring drainage by incision. In rare instances the process is more extensive and destructive, with cellulitis of the neck or erosion of important vessels in the neck and fatal hæmorrhage, or sloughing and widespread destruction of tissue.

(ii) *Otitis Media.*—The condition is not uncommon in scarlet fever. It is described, with other aural complications, in Chapter VI.

(iii) *Albuminuria and Nephritis.*—Apart from the febrile albuminuria during the initial toxæmia, damage to the kidneys usually manifests itself in one of three ways :—

(*a*) *Simple Albuminuria.*—The urine contains albumin, varying from a trace to a moderate amount. Microscopically, the urine contains a few casts, and occasionally a few red-blood cells. General disturbance is slight, although a little pyrexia is common

at the beginning. The albuminuria may be transient, or may persist for weeks. It usually disappears entirely.

(b) *Nephritis without Uræmic Manifestations.*—Less commonly the urine contains blood and albumen, the quantity passed is diminished, and the general disturbance is more marked than in (a). Although biochemical examinations reveal that retention of nitrogen exists, the clinical evidence of this is not striking. Œdema is usually slight and the blood pressure is not markedly raised.

(c) *Nephritis with Uræmic Manifestations.*—In the most severe cases, which are fortunately rare, evidence of kidney failure occurs. The urine is scanty in amount and contains blood, albumen and casts. Pyrexia, headache, vomiting, œdema, hypertension, twitchings and convulsions—and in the worst cases suppressed urine—may result in a fatal issue from acute uræmia.

There is no clear clinical division between these three degrees of kidney damage, although it is convenient to classify them as above. Generally, the kidney recovers entirely; occasionally the damage is permanent and results in chronic nephritis. As with the ears, so with the kidneys: if they have been previously damaged, an attack of scarlet fever is liable to involve them in a recrudescence of the inflammation.

The syndrome of acute nephritis, adenitis, and possibly otitis, occurring late in the attack was at one time very common.

(iv) *Arthritis.*—The types of joint pains which occur are :—

(a) Pains in the limbs occurring during the initial toxæmic and pyrexial period, and which are not peculiar to scarlet fever.

(b) *Acute Migrating Polyarthritis*, usually appearing after a latent period, and so closely resembling acute rheumatism that it has received the name of "scarlatinal rheu-

matism." These flitting joint pains are associated with pyrexia, and both respond to treatment with salicylates.

The heart may be involved. In a high percentage of cases a history can be obtained of previous acute rheumatic symptoms or of rheumatism in the patient's family. It is a recognised feature of acute rheumatism that an attack of acute streptococcal tonsillitis precipitates a recurrence of the disease after a latent period of ten to fourteen days. Since scarlet fever is a variety of streptococcal tonsillitis it can produce the same effect. The so-called scarlatinal rheumatism should therefore be considered and treated as being of truly rheumatic origin.

(*c*) *Acute Secondary Multiple Arthritis* usually localised in one joint as *suppurative* arthritis. Hæmolytic streptococci can invariably be cultivated from such septic joints. They are, in fact, a manifestation of septicæmia, and of grave prognostic import.

(*d*) Joint pains associated with serum sickness may occur in patients treated with scarlatinal antitoxin, but are uncommon with modern refined sera.

(v) *Carditis.*—The carditis which sometimes occurs is identical with that of acute rheumatism. It is predominantly an endocarditis which leaves permanent valvular lesions. The clinical and electrocardiographic evidence of involvement of the myocardium is similar to that seen in rheumatic fever. The carditis and the "rheumatism" of scarlet fever occur together; in young children the joint pains may be insignificant; in older patients the brunt falls upon the joints, and the heart frequently escapes. This, again, is like acute rheumatism. Similarly, the chorea which sometimes appears during the course of scarlet fever is rheumatic.

(vi) *Rhinitis and Sinusitis.*—Mucopurulent rhinitis is quite common, and it is probable that in many cases the accessory sinuses are also involved.

(vii) *Vaginitis.*—Vaginitis, or vulvo-vaginitis, causing mucopurulent discharge containing hæmolytic streptococci, is not uncommon and is probably the result of autoinoculation from the upper respiratory tract.

Rarer Complications.—Although there is evidence that transient *bacteriæmia* is not uncommon, *septicæmia* is a rarer event; and when it occurs, localisation in one or more organs is usual, resulting in *suppurative arthritis, osteomyelitis, meningitis, peritonitis* or *suppurative pericarditis* (distinct from the pericarditis of the rheumatic syndrome). If localisation does not occur, septicæmia runs the usual course with rigors, remittent temperature and severe toxæmia. Prognosis, which was always regarded as grave, has improved since the introduction of the sulphonamide group of drugs. If recovery occurs it does so only after a severe and prolonged illness. Sometimes septicæmia is secondary to aural complications. *Purpura hæmorrhagica, purpura fulminans* and other vascular complications, such as *gangrene* of the leg, are recorded.

Encephalitis, myelitis and *toxic psychosis* are of rare occurrence in adults.

Relapses and Second Attacks.—Relapses during the third to sixth week are attributed by some to a reinfection with a different serological type of hæmolytic streptococcus, and are most likely to occur in those who remain persistently Dick-positive, viz., those with a poor immunity mechanism, those who had mild attacks and those who have had antitoxin. In all of them the active acquired immunity is insufficient to protect against reinfection.

Second attacks of scarlet fever sometimes occur for the same reason.

Varieties of Scarlet Fever.—The ordinary type of scarlet fever described above may be *mild* or *moderate* in severity; rarely *severe* attacks occur. If the portal of entry is the skin instead of the respiratory tract the condition is *surgical scarlet fever.* In puerperal women, if the organism enters through the genital tract *puerperal scarlet fever* occurs; but if the portal is the respiratory tract, it is an ordinary case of scarlet fever occurring during the puerperium. Apart from this classification according to the portal of entry, varieties of scarlet fever are described depending upon the seriousness of some of the manifestations. In *septic scarlet fever* the striking features are the severity of the infection in the upper respiratory tract and the variability of the rash. The fauces are markedly congested; exudate is present on the tonsils and possibly

adjacent structures ; the mouth is dirty ; there is an offensive purulent, sometimes blood-stained discharge from the nose ; frequently the middle ears are involved, resulting in a profuse otorrhœa ; and the cervical glands are enlarged and tender and frequently suppurate. In some instances the rash, instead of being a punctate erythema, is a patchy erythema, most marked around the joints, and resembling erythema multiforme. There is a greater tendency to complications in this variety of the disease.

In *toxic scarlet fever* there is a preponderance of systemic manifestations. General and cardiovascular weakness, restlessness, delirium and semiconsciousness—in fact, all the features described under the typhoid state (see p. 38)—occur, associated with vomiting, hyperpyrexia and a dusky rash, indicative of a very severe attack.

A *hæmorrhagic* form is sometimes seen in adults in which, apart from the severity of the usual manifestations, there are hæmorrhages into the skin and mucous membranes and clinical signs of septicæmia.

The Diagnosis of Doubtful Cases of Scarlet Fever.—When the signs are insufficient to establish a diagnosis on clinical grounds alone, additional evidence can be obtained by carrying out tests :—

1. *Dick Test.*—At the beginning of an attack of scarlet fever the Dick test is positive. A negative result at this stage is therefore evidence, but not conclusive evidence, against the diagnosis. A positive result merely indicates that the patient is susceptible to the disease, not that he is suffering from it.

   In a high percentage of cases of scarlet fever the Dick test becomes negative before the twenty-first day. If the test is positive at the beginning of the illness and negative on the twenty-first day, this is strong presumptive evidence of an attack of scarlet fever (*vide* Chapter VIII).
2. *Swabbing for Hæmolytic Streptococci.*—Hæmolytic streptococci can almost invariably be isolated from the portal of entry. In the ordinary case of scarlet fever the throat and nose are swabbed ; in surgical scarlet fever, the suspected cutaneous lesion is examined ; in puerperal scarlet fever the genital tract is investigated bacteriologically. As hæmolytic streptococci are common in normal throats, too much reliance must not be placed upon a positive report,

particularly if the number of colonies obtained is few. A negative result is, however, strong presumptive evidence against the diagnosis if the possibility of some other portal of entry is excluded.

In surgical and puerperal scarlet fever swabbing should always be carried out, as the diagnosis depends upon finding streptococci *present* at the portal of entry and *absent* from the fauces.

Serological typing of hæmolytic streptococci is at present too complicated a procedure to be used as a routine in the diagnosis of doubtful cases.

3. *Schultz-Charlton Blanching Test.*—The rash of scarlet fever results from the action of the toxin on the cutaneous vessels, which become dilated. If the toxin is neutralised the rash disappears. In the Schultz-Charlton test 0·2 c.c. of diluted scarlatinal antitoxin is injected intradermally into an area of skin affected by the rash. In eight to twenty-four hours the rash is blanched over a circular area of about ½ to 1½ in. diameter around the site of the injection. This area of blanching persists until the rash disappears from the rest of the body. Subsequently, the blanched area either fails to desquamate or does so to a much less degree than the surrounding skin. If blanching occurs the test is positive, and the rash is scarlatinal. Unfortunately, the test is not invariably accurate. The main drawbacks to its employment are two. Firstly, it fails to blanch about 20 per cent. of scarlatinal rashes, particularly those which are three or four days old. Secondly, in faint and evanescent rashes, the very ones which may present clinical difficulties, the test may fail—in faint rashes because it may be impossible to find a suitable area of skin to carry out the test ; in evanescent rashes because the whole rash may have faded in twelve hours, the time when blanching is most pronounced.

The scarlatinal antitoxic serum employed is diluted with normal saline. According to the sample of serum, the dilution varies between 1 in 10 and 1 in 100. Sometimes convalescent (human) serum is used to avoid possible reactions from horse serum.

The student should note that in the Dick test scarlatinal *toxin* is used ; in the Schultz-Charlton test scarlatinal *antitoxin* is employed.

To sum up, at the beginning of the illness the diagnosis of a doubtful case is made on the clinical examination, the Dick test, bacteriological examination for hæmolytic streptococci and the Schultz-Charlton blanching test; later, a *retrospective* diagnosis may be made by clinical examination for the presence of desquamation and the reversal of the Dick test. The most important clinical rule is *never to make a diagnosis of scarlet fever on the rash alone.*

Differential Diagnosis.—At the onset it may be impossible to differentiate a commencing attack of scarlet fever from any other acute infection, but in twenty-four hours there is usually some positive evidence of the disease. The conditions which have to be differentiated are those which resemble the enanthem and those which may be confused with the exanthem.

Acute Tonsillitis.—It has already been stressed that there is no essential difference between scarlet fever and the ordinary hæmolytic streptococcal tonsillitis; but the differentiation must be made, as the former is a notifiable disease and the latter is not. Tonsillitis due to other organisms, such as pneumococci, occasionally resembles the faucal condition in scarlet fever. The presence of the typical rash of scarlet fever serves for differentiation.

Diphtheria.—Occasionally the deposit on the fauces in scarlet fever resembles diphtheria. In scarlet fever the exudate is soft, white and readily removed; in diphtheria it is a smooth, cream-coloured pseudo-membrane which is removed with difficulty, leaving a bleeding surface. Often the membrane in diphtheria extends beyond the tonsils. The rash of scarlet fever may be overlooked or may not be present at the time of the examination. Bacteriological examination is of assistance. In scarlet fever the hæmolytic streptococci are present in considerable numbers; in diphtheria the *C. diphtheriæ* can be isolated. If the rash is detected there is no difficulty in the diagnosis, although it must be remembered that scarlet fever and diphtheria are occasionally concomitant.

Scarlatiniformal prodromal rashes, seen occasionally in other infectious diseases, may be confused with scarlet fever. The diseases in which they most commonly occur are chickenpox, measles and smallpox. In all of them the Schultz-Charlton reaction is negative; swabs for hæmolytic streptococci are usually, but not invariably, negative; and the Dick test may be positive or negative. In chickenpox the early lesions of the characteristic rash are usually present with the prodromal rash, but must be looked for carefully. The scarlatiniform rash of chickenpox so closely resembles scarlet fever that for

a long time it was believed that such cases were double infections with scarlet fever and chickenpox. In measles and smallpox, scarlatiniform prodromal rashes are evanescent; and when the characteristic features of the disease appear, the prodromal rash disappears.

Rubella.—Typical cases of rubella present no difficulty, but the discrete macular rash sometimes changes its form on the second day and becomes scarlatiniform. The main points of difference between scarlet fever, rubella and measles are given in Table IX.

Measles.—Apart from the scarlatiniform prodromal rash, the characteristic rash of measles may resemble scarlet fever. The morbilliform elements, between which normal skin can usually be seen, may be so profuse and confluent as to produce a uniform area of erythema, thus causing difficulty. Usually, however, the essential nature of the rash can be seen on the extremities; the circumoral area is invaded, and Koplik's spots are usually present upon the buccal mucosa.

Lobar Pneumonia.—Occasionally in children the flushed skin and high temperature of lobar pneumonia is mistaken for scarlet fever, particularly when the consolidated lung is difficult to detect, *e.g.*, apical or central pneumonia.

Drug Rashes.—The commonest drug to produce a rash likely to be mistaken for that of scarlet fever is belladonna (atropine). The rash is usually a simple erythema and there is no enanthem; the pupils are dilated and the tongue dry. Quinine, aspirin and iodides may also be responsible.

Serum Rashes.—Serum rashes are occasionally scarlatiniform. Usually such an appearance is only a phase in a changing rash. Urticarial elements appear either at the same time or at some other stage of the eruption. There is a history of the administration of foreign sera and there is no enanthem.

Skin Diseases.—Exfoliative dermatitis and pityriasis rubra pilaris are two rare protracted skin conditions which may be mistaken for scarlet fever because redness and scaliness of the skin occur in both. Acute sunburn may also be mistaken for it, as peeling commonly occurs after the redness has gone.

Treatment.—The general nursing of scarlet fever conforms with the principles laid down in Chapter X. The patient should be confined to bed until the temperature has been normal for seven days, providing no complications are present. No modifications of the ordinary fever diet is necessary, although a very low protein diet and the exhibition of alkali is sometimes recommended to prevent nephritis.

Serum Therapy. — Scarlatinal antitoxin (antiscarlatinal

TABLE IX

	Scarlet Fever	Rubella	Measles
Constitutional disturbance including pyrexia	Moderate	Slight or absent	Moderate.
Coryza	Absent	Slight or absent	Definite.
Cough	Absent	Rare	Present.
Fauces and mouth	Tonsillo-pharyngitis. Typical tongue	Usually insignificant changes	General injection. Koplik's spots.
Rash: TYPE	Punctate erythema	Discrete macular	Fusing maculo-papular, blotches, etc., with normal skin between.
COLOUR	Scarlet	Pink	Dull red.
DISTRIBUTION	General, except face. Face flushed; circum-oral pallor	General, including circum-oral region	General, including circum-oral region.
Other points	Pastia's sign	Posterior cervical glands enlarged. Rash changes form — quickly fades	...
Tests	Dick-positive, becoming negative. Swab for streptococci positive. Schultz-Charlton blanching	Türck and plasma cells in blood	...

serum) has a definite effect upon the initial toxic manifestations. From twenty-four to forty-eight hours after its administration the general toxic symptoms and the pyrexia subside, the rash disappears and the faucial angina abates. Desquamation either does not occur or is minimal. Many believe that serum also tends to diminish the incidence of complications.

The earlier serum is given, the more marked are its effects. It is often administered as a routine to the mild cases of scarlet fever, which constitute such a high percentage of the cases to-day, chiefly because it diminishes desquamation and so permits earlier discharge from isolation without social disability. The usual dose is 10 c.c. of concentrated scarlatinal antitoxin or 3 c.c. of globulin-modified (protein-digested) antitoxin given intramuscularly. Severe cases require from twice to four times these doses by the intravenous route.

The standardisation of scarlatinal antitoxin is unsatisfactory. The *unit* is the smallest amount which neutralises fifty skin-test doses of toxin (see p. 97). Expressed in units, the therapeutic dose varies between 9,000 and 36,000.

Antitoxin has little or no effect upon complications ONCE THEY ARE ESTABLISHED.

Drugs.—Sulphonamides should be used for the *invasive* features of the disease, especially in conjunction with scarlatinal antitoxin.

Aspirin in 10-gr. doses is useful at the onset for the sore throat, headache or general pains, particularly in older patients.

Local treatment of the throat by syringing is considered undesirable.

Treatment of Complications.—Apart from the sulphonamides, the treatment of complications follows the usual lines, *e.g.* :—

Adenitis : Local heat by poultices, antiphlogistine, etc. ; if suppuration occurs, incision and drainage.

Otitis Media (*vide* Chapter VI).

Albuminuria and nephritis : Restriction of proteins and salt in the diet, and regulation of the fluid intake ; blankets next to the skin ; measures designed to increase the activity of the skin and bowels without exhausting the patient, *e.g.*, sponging. Daily measurement of the quantity of urine and the amount of albumen passed and the amount of fluid taken must not be omitted. The treatment of uræmia follows the usual lines.

(Patients with complications are better barrier-nursed or isolated.)

Fatality Rate.—The fatality rate in scarlet fever is at present about 0·5 per cent.; the rate is higher in younger children and lower in adults. Uncomplicated scarlet fever does not kill, except in the rare toxic and hæmorrhagic type. Most deaths are due to complications, such as meningitis following middle-ear infection, uræmia supervening on acute nephritis, septicæmia with or without local suppurative lesions, broncho-pneumonia and empyema.

Pathology.—In the toxic and hæmorrhagic cases the appearances post-mortem are those of a severe toxæmia or septicæmia, and there are no changes characteristic of the disease. The heart musculature is pale and soft and the blood unduly fluid; there is congestion of the bases of the lungs; the liver and spleen are soft; the kidneys are dull and opaque from cloudy swelling; petechial hæmorrhages occur under the serous membranes; the fauces present the changes seen in life; the rash, except for hæmorrhages and pigmentation, disappears at death. When complications cause death the morbid changes are those of the complication. Kidney complication produces an interstitial cellular infiltration around the tubules with evidence in the more marked cases of nephritis of particular damage to the glomeruli (a glomerular nephritis). On section the kidney may ooze blood. The changes found in carditis are similar to those in acute rheumatism.

Infectivity and Mode of Transmission of Scarlet Fever.—Hæmolytic streptococci are present in the nasopharynx, fauces and any discharges. The ordinary case is most infectious in the early stages. With the fall of the temperature infectivity declines, and by the third or fourth week most cases can safely be released from isolation. Nevertheless, in a high percentage of them the organism can still be isolated from the nasopharynx. Freedom from infection is therefore judged mainly on clinical grounds. If there is any abnormality of the fauces of pharynx, if any discharges are present from the nose, ears, etc., or if any complications such as cervical adenitis are present, the patient must be considered as potentially still infectious. Desquamation is not infectious, although it is not desirable to allow the patient to return to his ordinary life if he is still desquamating freely. In special circumstances it may be desirable to ensure freedom from hæmolytic streptococci by release cultures taken from the nose and throat.

Some patients remain infectious for a variable period after recovery has occurred, *i.e.*, they become *convalescent carriers.* The types of patient most likely to do so are those who have

had complications such as rhinitis, otitis media or cervical adenitis, and those who have some old abnormality of the upper respiratory tract such as chronically enlarged tonsils and adenoids or abnormal nasal conditions.

Apart from convalescent carriers, *contact carriers* occur. They harbour the hæmolytic streptococci of scarlet fever, although they have not had the disease.

Scarlet fever is transmitted by the infectious droplets and discharges of patients or carriers. The transmission to the new host may be direct or indirect. In direct transmission the infectious material may be inhaled, causing the ordinary type of scarlet fever; or it may be inoculated, producing surgical or puerperal scarlet fever. Indirect transmission is much less common. Milk may be infected by a carrier and cause explosive outbreaks of the disease. In hospital, an attendant may transmit the disease on her hands, clothing or instruments. Transmission by inanimate objects and fomites is rare

Return Cases.—When patients who have recovered from scarlet fever return to their homes from hospital, they occasionally give rise to scarlet fever in other members of the family. The new cases are termed *return cases* and the culprit, who is really a *convalescent carrier*, is termed an *infecting case*. It is a convention to regard all new cases arising within a month as return cases, although it is obvious that many, particularly those occurring after the first week, may have been infected elsewhere. The return case rate ranges from 2 to 4 per cent. of discharged patients.

INFECTIOUS SORE THROAT

Infectious sore throat may be caused by a number of organisms, but is usually due to the hæmolytic streptococcus. The general symptoms and the appearance of the fauces are precisely similar to those described in scarlet fever. The only clinical difference between the two diseases is the occurrence of a rash in scarlet fever. Its absence in infectious sore throat may be due to one of two causes :—

(*a*) The hæmolytic streptococcus responsible for the infection may be a variety which does not produce erythrogenic toxin. The disease, when transmitted by droplets to the respiratory tract of other individuals, breeds true, causing only sore throat.

(*b*) The patient is Dick-negative. In such cases, if the infecting strain produces an erythrogenic toxin, its effect when transmitted to other individuals will

depend upon their antitoxic immunity. If they are Dick-positive, the infection will cause scarlet fever; if Dick-negative, a simple attack of tonsillitis. In every outbreak of scarlet fever a number of such infectious sore throats occur among Dick-negative contacts.

SUMMARY OF SECTION II

Scarlet Fever: Ordinary, surgical, puerperal.
Symptoms: Headache, sore throat, vomiting.
Signs: Pyrexia, enanthem (tonsillitis and strawberry tongue), exanthem (punctate erythema) with circum-oral pallor and subsequent desquamation.
Aids: Dick test, Schultz-Charlton blanching test, swabbing and plating for hæmolytic streptococci.
Infectious Sore Throat: Equivalent to scarlet fever without the exanthem.

III. ERYSIPELAS

Definition.—An acute local hæmolytic streptococcal infection of the skin, characterised by a spreading circumscribed patch of erythema and general toxic symptoms.

Ætiology.—The organism is present in the lymph spaces of the skin at the site of the local lesion and in the lymphatic vessels beyond the spreading margin. The disease affects persons of all ages, although it is most common in those over forty years. Chronic diseases of the arteries, kidneys, lungs and liver, chronic alcoholism and general debility predispose to the disease. In the past, outbreaks were not uncommon in surgical wards, in old hospitals and in overcrowded institutions where facilities for preventing the spread of infection were primitive. To-day the disease is usually sporadic. Its infectivity is relatively low. The case fatality rate is greatest in the extremes of life. Formerly about 5 per cent. at all ages, this figure is no longer relevant as modern treatment with the sulphonamide group of drugs has materially diminished the rate.

The hæmolytic streptococcus enters through a breach in the skin. The portal may be obvious, such as a surgical wound, a vaccination pustule, an ulcer of the leg or the stump of the umbilical cord in a new-born infant; or relatively insignificant, such as a crack in the nares or behind the ear, a fissure at the inner canthus of the eye, a pin scratch or a scratch pimple; or it may be too small to be visible to the

naked eye, as in the so-called *idiopathic* type, which is by far the commonest. Although the infection may be derived from some exogenous source, in a large number of cases it is endogenous—an auto-inoculation from a streptococcal infection of the fauces, nose, sinuses, middle ear, etc.

Incubation Period.—The incubation period is variable, **one** to **seven** days being common limits.

Clinical Features.—The onset is abrupt with shivering, headache, malaise, vomiting, pyrexia and generalised pains. Within a few hours, the local lesion appears at the site of inoculation and gives rise to an unpleasant sensation of tightness in the skin. The lesion consists of a raised, tense, glistening area of erythema with a border which in most cases is well defined and palpable as a smooth ridge. The red plaque spreads centrifugally, the advancing margin indicating the site of the greatest activity of the inflammatory process. Where the connective tissue of the skin is lax, as in the eyelids, vulva and scrotum, considerable swelling occurs and the spread of inflammation is rapid. Where the skin is tight, as over the front of the legs and cartilage of the pinna, swelling is less and the spread is retarded ; but pressure from the inflammatory œdema may produce necrosis of the skin. Superficial, thin-roofed bullæ containing seropurulent fluid are common on the erythematous area.

The *general symptoms*, which are due to toxæmia, vary from a slight indisposition with a trivial pyrexia of 99° or so to a severe " typhoid " state with prostration, delirium, pyrexia of 104° to 105°, and a rapid, soft pulse of 100 to 120. The general condition at the height of the disease depends, not only upon the severity of the attack, but also upon the age and previous condition of health of the patient. In infants and in elderly subjects, particularly those who are debilitated or are suffering from chronic disease, the constitutional disturbance is more likely to become severe than in children and young adults. The danger lies in the possible development of grave, sometimes fatal, toxæmia, or of one of the complications mentioned below.

Generally, the local lesion spreads for three to six days and then begins to regress. The subsidence of the inflammation may be uniform, or, more commonly, the oldest part of the lesion, the centre, fades first. Sometimes this occurs whilst the edge is still advancing. A little desquamation and pigmentation are sometimes left after the plaque has disappeared. If bullæ are present, crusts usually form, but, as a rule, no scarring follows their separation. The general

symptoms usually subside when the local lesion ceases to spread.

Facial erysipelas is the commonest type. Often the portal of entry of the organism cannot be detected. The lesion frequently starts near one of the mucocutaneous junctions: in the vicinity of the nose, the inner canthus of the eye or the external ear. Although it may be confined to one side of the face, it usually spreads across to involve the butterfly area—the cheeks and the nose. When fully developed the whole face is reddened and swollen. The eyelids are so œdematous that the palpebral fissures are obliterated, the eyes cannot be opened and there is a little mucopurulent conjunctival discharge. The ears are thickened and the scalp swollen. Blebs are common on the ears, eyelids and forehead. The regional lymph glands are enlarged and tender. The fatality from erysipelas of the face is, however, less than that of the extremities.

Erysipelas migrans is an unusual type, seen most commonly in infants, the feature of which is the tendency for the local lesion to "wander" over the body. In the worst cases the process migrates from the face to the greater part of the body.

Complications.—The typical erythematous plaque of erysipelas is due to an inflammatory process involving the true skin. Not infrequently, and more commonly on the extremities than on the face, the subjacent subcutaneous tissue may be involved, producing an *erysipelo-cellulitis.* Suppuration may occur in the subcutaneous tissue in the form of one or more small, localised abscesses, or as a more wide-spread abscess involving the whole site of the disease.

The organism in the local lesion sometimes involves the blood stream directly, producing *septicæmia*. *Pyæmia* is rarer, and is more likely to occur if suppuration and venous thrombosis have complicated the picture. *Infective endocarditis* and *meningitis* from direct spread from the scalp are also described.

The local lesion may spread from the skin to adjacent mucous membranes. Rarely this may cause *acute œdema of the glottis*.

Broncho-pneumonia is an occasional cause of death, particularly in elderly patients subject to chronic bronchitis.

A true *acute nephritis* also occurs and is distinct from the albuminuria which is a common manifestation of the toxæmia, especially in older patients.

Relapses and recurrences are common. Stevens (1933) attributes them to hæmolytic streptococci persisting in the nose from a chronic sinusitis.

Treatment.—The value of the sulphonamide group of drugs is established. Streptococcal antitoxin, ultra-violet radiation and local application have been supplanted. The dose of sulphonamide is that given on p. 83. For most cases the dosage described for moderately severe or mild infections is sufficient. Within forty-eight hours of administration the temperature usually subsides and the lesion ceases to spread ; thereafter improvement is usually rapid—the local lesion fading and the toxæmia disappearing. To avoid relapses, the drug should be continued for a few days after clinical signs have disappeared.

Simple bathing of the eyes is necessary in facial erysipelas, particularly when the palpebral fissure is obliterated by swelling. Hot fomentations or other measures for producing local heat provide relief. Sulphates, either as aperients or as compresses should be avoided (see Sulphonamides, pp. 83, 84). For the ordinary facial attack no covering is necessary.

Symptomatic treatment for restlessness, delirium and other manifestations of toxæmia may be necessary.

SUMMARY OF SECTION III

Local signs : Circumscribed patch of erythema with raised palpable margin ; bullæ sometimes present.
General signs : of toxæmia.
Treatment : Sulphonamides.

IV. PUERPERAL SEPSIS

(Including *Puerperal Fever*)

Definition.—Puerperal sepsis includes a number of diseases resulting from infection of the female genital tract during labour or the puerperium, or during a miscarriage or abortion. Although organisms may enter through various parts of the genital tract, the placental site is the most vulnerable area. The diseases produced vary from a trivial local lesion to a severe and frequently fatal septicæmia. To the obstetrician the puerperium is the period between the end of labour and the return of the genital tract to normal, usually about six weeks ; but the Public Health authorities are concerned only with those infections arising within twenty-one days after

birth which require to be notified as cases of *puerperal pyrexia*. The definition of this condition is "any febrile condition occurring in a woman within twenty-one days after childbirth, or miscarriage in which a temperature of 100·4° F. (38° C.) or more has been sustained during a period of twenty-four hours, or has recurred during that period." This pyrexial standard may exclude a number of true puerperal infections. In London *puerperal fever* is compulsorily notifiable.

Ætiology.—In the middle of the nineteenth century Semmelweiss, investigating the appalling fatality of women delivered in institutions, came to the conclusion that puerperal fever was infectious. Even so, it was for long believed that, in most cases, the source of infection was the patient herself. Puerperal infection remained the chief cause of maternal mortality and for many years attempts to diminish its incidence and fatality were attended with little success, but there is now evidence that the attack on the disease is succeeding. The emphasis laid upon the external origin of infection, and the support for this view provided by modern knowledge of the types of hæmolytic streptococci responsible for the disease, have influenced obstetric practice and the laws governing it enormously, and have contributed materially to the prevention of puerperal infections. Furthermore, the sulphonamide group of drugs recently introduced holds out hope of recovery in even the worst cases.

Bacteriology.—*Hæmolytic streptococci* are responsible for 40 per cent. of cases of puerperal fever (L. Colebrook, 1938) and produce the most virulent and, until lately, the most fatal forms of the disease. Before the introduction of the sulphonamide group of drugs, fatality rates as high as 68 to 90 per cent. were recorded in cases with septicæmia. At Queen Charlotte's Hospital a reduction of the rate from 22·8 to 5·5 per cent. has been effected by the use of the drugs (L. Colebrook, 1937). It must be understood that not all hæmolytic streptococcal infections are severe; most of them are mild (*vide infra*, Pathology). The hæmolytic streptococci do not belong to a special type. Many are identical with streptococci found in other morbid conditions, or present in the upper respiratory tract of carriers. They do *not* correspond in type with those occasionally found in the vaginæ of healthy women.

Next in importance as a cause of fatality are *anaerobic streptococci*. Other organisms such as *staphylococcus aureus*, *B. coli.*, *gonococci* and *pneumococci* are sometimes responsible for morbidity and fatality.

Sources and Modes of Infection.—The source of the causal organisms may be :—

1. EXTRINSIC, *i.e.*, they are introduced from outside the genital tract. They may be derived from some other part of the patient's body (*autogenous*), or from some other person or object (*heterogenous*).
2. INTRINSIC, *i.e.*, they are present in the genital tract and gain access to the tissues during labour and the puerperium.

The normal pregnant uterus is sterile ; the vagina, however, contains a variety of organisms. Streptococci have been found in a small percentage of cases, but do not correspond in type to those found in puerperal disease, and are therefore not regarded as causal. Most cases, particularly those due to hæmolytic streptococci, are now believed to be of *heterogenous* origin. The organisms are conveyed to the genital tract on instruments or the hands of attendants or by droplet spray from the upper respiratory tract of a carrier in attendance. The droplets may be sprayed on to the perineum, or upon "sterile" instruments or hands. The chief *autogenous* sources are the upper respiratory tract, the bowel and the skin of the perineum. Much less importance is now attached to foci of sepsis, such as teeth and tonsils, as a direct cause of puerperal infection than was the case formerly. The *order of frequency* of extrinsic sources is (*a*) an attendant, (*b*) a member of the mother's household, (*c*) the mother herself.

In most cases, therefore, the organism gains access by *inoculation* of a wound of the genital tract. In normal labour, small lacerations of the perineum, vagina and cervix are common ; in the uterus the raw placental site, with its large open venous sinuses and enlarged lymphatic spaces, provides wide channels for the entry of organisms. Where labour has been difficult or instrumental, the breaches are more numerous, and interference increases the chances of infection. Two factors determine the nature and severity of the resulting disease ; on the one hand the type of organism, its invasive power and its capacity to produce toxin ; on the other the site of entry and the resistance of the patient, both local and general. Predisposing factors are exhaustion due to prolonged and difficult labour, loss of blood and trauma, which includes both lacerations and bruising. The site of entry is important : most of the severe and generalised infections are secondary to an infection of the placental site.

Pathology.—The following types of puerperal sepsis may occur :—

1. CIRCUMSCRIBED LOCAL LESIONS AT THE PORTAL OF ENTRY.—Infection of wounds of the perineum, vulva, vagina or cervix may cause a circumscribed inflammatory lesion. Septic raw areas, ulcers with a membranous base, swelling and pus formation occur. General disturbance results from the absorption of toxins ; it is seldom severe. With hæmolytic streptococcal infections, an erythrogenic toxin in a Dick-positive subject may cause a scarlatiniform rash and the patient suffers from *puerperal scarlet fever*. The septic local lesion may be overlooked, but on swabbing hæmolytic streptococci are found.

   A local infection of the *uterus* assumes special importance (formerly it received a special name—*sapræmia*). The puerperal uterus always contains dead tissues, *e.g.*, necrotic decidua, blood clot and fibrin ; occasionally small fragments detached from the placenta or membranes remain attached to the uterine wall. In such dead tissue organisms find a suitable nidus and toxins elaborated may enter the circulation. Every infection causes an inflammatory reaction of variable degree in the lining and wall of the uterus (*endometritis* and *metritis*) which may be localised to the placental site or generalised. A barrier to the advance of the disease is thereby set up which varies with the causal organism. Hæmolytic streptococci cause less response than *B. coli* and anaerobic organisms, and, with the last two, spread is less likely.
2. LESIONS DUE TO DIRECT EXTENSION FROM THE PORTAL OF ENTRY.—Spread from the initial lesion follows one or more of three paths :—

   (i) Via the *lymphatics* : Local lymphangitis and cellulitis is set up, which sometimes suppurates ; occasionally the organisms reach the general circulation through the lymphatic duct.

   (ii) Via the *veins* : phlebitis results which may cause thrombosis (*thrombophlebitis*). The infection may spread from the small veins of the uterus to the pelvic plexuses, or the main veins (iliac, inferior vena cava). *Periphlebitis and suppuration* occasionally follows.

From the infected vein the organism may enter the blood stream directly, or fragments of infected clot may be detached and enter the circulation.

(iii) Via the *mucous membrane*: direct extension from the uterus to the Fallopian tubes, ovaries and peritoneum more commonly follows abortion than " term " cases.

The clinical conditions which result may be one or more of the following :—

Parametritis (pelvic cellulitis) is usually lymphatic, less commonly phlebitic in origin. It spreads usually from an infected cervical lesion. The hard inflammatory mass in the cellular tissues may recede or suppurate.

Pelvic peritonitis may advance to *general peritonitis*. The peritoneum may be involved via the lymphatics or from small abscesses of the uterine wall secondary to suppurative thrombophlebitis, or from direct extension along the tubes.

Salpingitis or *salpingo-oophoritis* follows direct extension along the mucous membrane.

Thrombophlebitis of the pelvic, iliac or femoral veins is sometimes the pronounced clinical feature.

Urinary infections, *e.g.*, cystitis, are not uncommon in pelvic infections because of the proximity of the urinary to the genital tracts.

3. GENERAL INFECTIONS.—*Septicæmia* may be of *phlebitic* or *lymphatic* origin. The resulting syndrome varies. With lymphatic spread, only organisms enter the circulation and there is a greater likelihood of endocarditis and serositis (pericarditis, meningitis, suppurative arthritis, pleurisy). With venous spread, whilst organisms alone may enter the circulation, there is also the possibility of infected thrombi circulating and causing *pyæmia*. Septicæmia may occur with or without an obvious septic focus in the pelvis. The latter (" primary " type of septicæmia) indicates invasion of the organism and/or poor resistance by the patient.

Clinical Features.—The student is referred to textbooks of gynæcology for a full account of the clinical conditions enumerated above. It will suffice here to describe briefly the

chief symptoms which suggest that the puerperium is not proceeding normally.

Pyrexia is so constant and important a sign that notification has been made dependent upon its presence. Its appearance necessitates *immediate* clinical and bacteriological examination. A high vaginal swab suffices. Bacteriological examination of the interior of the uterus or of the cervix provides little additional information and may be dangerous. If pyrexia is considerable or persistent, or if rigors occur, a blood culture is necessary. The urine should also be examined clinically and bacteriologically.

Changes in the lochia. The discharge is usually profuse and fœtid ; it may remain so or become scanty and practically odourless when the saprophytic organisms are killed off. Scanty or suppressed lochia is evidence of severity and is the usual feature in fulminating hæmolytic streptococcal infections.

The *uterus* is bulky and tender and there may be a little abdominal distension. Of *general symptoms*, malaise and anorexia are most common.

Rigors are an important and serious sign that the infection is passing the local inflammatory barrier and " showers " of organisms are entering the circulation.

Treatment.—The nursing and diet conform with general principles laid down in Chapter XI. In order to facilitate drainage of the uterus, the patient should be propped up in Fowler's position and ergot exhibited. The bladder should be watched to avoid overdistension and infection.

Curettage and douching are contraindicated, but if there is evidence of retained products they may be removed digitally under an anæsthetic.

Glycerin, introduced into the uterus by catheter, stimulates the flow of secretions and helps to flush out the interior of the uterus. Once in position, the catheter is retained for twenty-four to forty-eight hours and glycerin introduced three or four-hourly in quantities of 10 to 20 c.c.

The *sulphonamide* group of drugs are of particular value in puerperal infections due to hæmolytic streptococci. Dosage should be that prescribed for severe or moderately severe infections (see p. 83) depending upon the severity of the attack.

Streptococcal antitoxic serum (*globulin-modified*) in doses of 5 to 20 c.c. intravenously helps to combat toxæmia in hæmolytic streptococcal infections, but has little or no influence on the dangerous invasive features. It may be considered as an adjuvant to the sulphonamides.

Blood transfusions and *immuno-transfusions* combat the anæmia and provide antibodies. Combined with sulphonamides they offer the best prospects of recovery in severe septicæmias.

Prophylaxis.—There are two chief aspects of prevention: to ensure, if possible, a normal labour, and to exclude extrinsic sources of infection. *Antenatal supervision* is of paramount importance in planning a normal labour and removing sources of infection in the mother. Labour should be conducted with strict regard to *asepsis.* Unnecessary vaginal examination, interference with the normal conduct of labour and bruising of the tissues should be avoided as far as possible. Attendants must wear *efficient masks.* Carriers of hæmolytic streptococci must be excluded from obstetric practice until swabs of the nose and throat are negative. Persons with septic lesions, *e.g.*, sores, paronychia, impetigo, must be prohibited from attending parturient women. No one with an infection of the upper respiratory tract, *e.g.*, "cold" or sore throat, must be permitted to approach the mother. Patients in maternity wards suffering from pyrexial conditions must be removed. In no other condition are prophylactic measures more life-saving than in puerperal sepsis.

SUMMARY OF SECTION IV

Sources of Infection:

1. Extrinsic: heterogenous and autogenous.
2. Intrinsic.

Mode of Infection: Inoculation of placental site or of wounds of the genital tract.

Types of Disease:

(*a*) Purely local.
(*b*) Local spread (by veins, lymphatics or mucous membranes).
(*c*) Generalised infections.

Early clinical signs: Pyrexia, changes in the lochia.

Treatment: Uterine drainage; sulphonamides; immuno-transfusions.

Prophylaxis: Antenatal supervision; normal labour with aseptic precautions; exclusion of sources of infection in attendants.

CHAPTER XIII

DIPHTHERIA

DEFINITION.— A local infection by virulent strains of *Corynebacterium diphtheriæ*, resulting in toxæmia. The clinical local lesion, which occurs at the portal of entry, usually some part of the respiratory tract, is a distinctive pseudo-membrane. The toxin produced locally and disseminated generally has an affinity for cardiac and nervous structures causing myocardial changes and paralyses at different stages of the illness.

Incidence.—The disease is endemic, with seasonal and local variations and epidemic phases. There has been a progressive decline in the incidence, death rate and case fatality in the last fifty years for which three factors are in large measure responsible—*early diagnosis*, the introduction of treatment by *antitoxin* and *active immunisation* of susceptibles. A factor of some importance in the incidence and severity of the disease is the prevalent type of bacillus (see Bacteriology).

The maximal seasonal incidence occurs in autumn and winter. There is little difference in sex incidence, although females are slightly more frequently infected, whereas the male fatality rate is slightly higher. The disease is most common between the ages of one and ten years. For the first six months or so of life a large percentage of infants retains some measure of their infantile immunity, and are therefore rarely affected. After ten years of age the disease declines in frequency, although adults are not uncommonly affected.

Diphtheria is most dangerous to the young, and the case fatality rate decreases with the age of the patient.

Bacteriology.—The causal organism is the *Corynebacterium diphtheriæ* (diphtheria bacillus, Klebs-Loeffler bacillus). Several classifications of diphtheria bacilli have been formulated according to morphological appearances, fermentation reactions (capacity to ferment carbohydrates) and, most important of all, biological tests for virulence. There is some correlation between these three classifications and the type of disease produced (see Table X), but it is not complete.

TABLE X—CHARACTERS OF *C. DIPHTHERIÆ*

	All Diphtheria Bacilli	Gravis Strains	Intermedius Strains	Mitis Strains
Morphology	Slender rods with slightly bulbous ends Metachromatic granules (polar bodies) Arrangement in Chinese letters Tendency to involution forms	Short; uniform staining; poor in metachromatic granules	**Barred. No metachromatic granules** when grown in tryptic serum agar	Usually "typical" as in second column.
Colony appearance on copper-tellurate	Colour: grey or black or combinations of these Margin: crenated or smooth	Grey rosette; rough	**Flat; grey; definite halo around a black centre**	Black; convex, smooth and shining.
Fermentation reaction	**Glucose: +** **Saccharose: 0**	**Starch: +**	Starch: 0	Starch: 0.
Virulence *	Some virulent, some avirulent	**Virulent,** almost always	**Virulent,** almost always	10 to 15 per cent. non-virulent.
Type of disease produced	Mild, moderate, or severe	Percentage of cases which develop fatal or severe attacks, **higher than in any of others**	Intermediate between gravis and mitis, but closer to gravis	Percentage of cases which develop fatal or severe attacks, **low.**

+ = Fermentation. 0 = No fermentation. **Heavy type: constant findings.** Ordinary type: variable findings.
* *N.B.*—Virulent diphtheria bacilli may be gravis, intermedius or mitis, but non-virulent organisms are usually mitis.

Typically, the organisms consist of rods, straight or slightly curved, usually rounded or a little bulbous at the ends. By using suitable stains, metachromatic granules (small bodies staining a different colour from the rest of the organisms) can usually be detected in the body of the bacillus. They number 1 to 6, but most frequently there are two situated one at each end of the bacillus, which is then described as presenting polar staining. Variations in morphological appearance are, however, common, not only in the length and in the appearance in the ends but also in the staining. Sometimes the organism stains uniformly (solid type) ; sometimes it presents a barred appearance ; sometimes the metachromatic granules are distributed along the body of the bacillus. In smears made from cultures, the arrangement of the organisms is often very suggestive. Pairs of organisms lying parallel with one another, organisms bent into a V or L shape, and organisms crossing one another when clumped together give an appearance of Chinese letters. In older cultures irregular forms (involution forms) frequently appear, the commonest being club shaped.

Other corynebacteria, the diphtheroids, have a similar morphology and are likely to be mistaken for diphtheria bacilli—particularly when cultured from sites which are commonly examined for diphtheria bacilli, *e.g.*, the nose. Usually diphtheroids exhibit morphological appearances, slightly different from diphtheria bacilli ; sometimes, however, they are indistinguishable, and it then becomes necessary to carry out further tests for the more complete identification of the organism. Diphtheroids are frequently found in the nose, ear, eyes and vagina, and less commonly in the throat.

Diphtheria of the nose and throat is common, and in a patient suspect on clinical grounds, the presence of organisms with the morphological characters of the diphtheria bacillus is usually sufficient bacteriological confirmation. Diphtheria of the ear, eye and vagina are, however, rare, and diphtheria-like organisms found in these situations should *invariably* be submitted to further tests. Tests for the fermentation of sugars, the appearances of colonies on special media (such as copper-tellurate) and virulence tests performed on guinea pigs are the most important of these additional investigations.

Some organisms, with all the morphological, cultural and sugar reactions of true diphtheria bacilli, *are incapable of causing the disease in man,* because they are *non-virulent.* They are sometimes isolated in cultures, and it is of the utmost importance to distinguish between them and the *virulent* type

of organism. This most important classification can only be made with certainty by *virulence tests* performed on guinea pigs by the intradermal method.

Suspensions of the organism to be tested are injected in parallel into the epilated abdomen of the animal partially protected by antitoxin. Virulence is shown by local redness and induration in from twenty-four to forty-eight hours.

A further division of diphtheria bacilli into three types—*gravis*, *intermedius* and *mitis*—is possible because of differences in their behaviour to starch and in the appearance of the colonies on special media (see Table X). The starch fermenters, as their name *gravis* implies, tend to produce a higher percentage of serious cases than the others. It should be emphasised that the severity of an attack of diphtheria depends not only upon the type of organism but also upon the resistance of the patient. An infection with a gravis strain in a fairly resistant individual may produce a moderate or a mild attack; but if patients could be selected with the same degree of resistance, gravis infections would produce the most serious type of the disease, intermedius a less severe attack and mitis the mildest of all. It is therefore important, in assessing the severity of an outbreak of diphtheria, and the value of prophylaxis and treatment, to know the prevalent type of diphtheria bacilli.

Many of the harmful effects of diphtheria bacilli are due to a soluble exotoxin which they secrete into the medium in which they are growing or into the tissues around them. No matter what the type of diphtheria bacillus may be, the toxin produced is exactly the same and is neutralised by antitoxin. Diphtheria bacilli vary considerably in their capacity to elaborate toxin, and the virulence or otherwise of the organism, as determined by guinea pig tests, depends largely upon this. Gravis strains are *not* necessarily better toxin producers, so that the cause of their greater pathogenicity must be sought for in some other property of the organism, such as invasive power. Diphtheria toxin is an unstable substance. It deteriorates rapidly as the result of keeping, and the action of heat and chemicals. A temperature of 75° C. maintained for ten minutes destroys it. One of the products of deterioration of toxin is *toxoid*, used for inducing active immunity (see Immunisation). Diphtheria toxin has never been isolated in pure form. The filtrates containing it are obtained by growing diphtheria bacilli in a fluid medium and filtering off the organisms. These filtrates

contain, in addition to the toxin, products of its deterioration such as toxoid, products of bacterial disintegration and substances contained in the medium. Nevertheless, the amount of toxin in such filtrates can be accurately determined. Formerly toxin was standardised by its lethal effect on guinea pigs, which are extremely susceptible to its action. A *minimum lethal dose* (M.L.D.) was the least quantity of toxin which would kill a guinea pig of 250 gm. weight in four days. Now the minimum reacting dose (M.R.D.) is employed: it is the least quantity of toxin necessary to produce a definite local reaction in the skin of a guinea pig. The M.L.D. is approximately equivalent to 500 M.R.D.

Pathology.—The characteristic feature of the local lesion of diphtheria is the presence of a "membrane" on the inflamed mucosa. It is produced only in the presence of the causative organism. Diphtheria bacilli, having been deposited on the mucosa, do not penetrate deeply, but multiply on the surface and produce toxins which diffuse into the neighbouring tissues. The mucosa responds with an inflammatory, exudative and necrotic reaction. Fluid exudes from the vessels and coagulates on the surface and between the superficial cells. In the *stratified* epithelium of the fauces and pharynx the superficial cells coagulate and necrose, and are entangled in the network of fibrin formed by the coagulating fluid: sometimes blood vessels are involved. The membrane thus consists of fibrin, necrotic epithelial cells, leucocytes, granular debris, diphtheria bacilli, a variety of other organisms and sometimes blood. Since the superficial layers of the mucosa constitute part of the membrane, the latter is firmly adherent. If it is torn off, a little bleeding occurs, and the membrane reforms. When recovery takes place the membrane separates in from one to seven days, sometimes later.

Usually there is no gross evidence of the loss of the superficial cells; but in the worst cases where the process has been deeper, particularly if there has been a secondary infection with hæmolytic streptococci, an ulcerated surface is exposed, but ultimately heals.

In the larynx, trachea and bronchi, where the epithelium is *ciliated*, the lining cells are incorporated in the "membrane" only at a few points, so that the membrane is *croupous*, *i.e.*, loosely attached to the surface, and consists mainly of fibrin and leucocytes. It should be remembered, however, that over the true vocal cords and the epiglottis stratified epithelium is found, and here membrane is likely to be more adherent.

Toxin is produced continuously at the site of the membrane

and passing into the lymphatic and blood streams, circulates generally and reaches the tissues. The amount of toxin produced and absorbed varies with the site, extent and character of the local lesion. Naturally, the larger the toxin factor, *i.e.*, the greater the extent of the membrane, the more toxin is produced. Absorption is easier from the pharynx than from the tonsils, and easier from the tonsils than from the larynx and trachea. In consequence, diphtheria in different situations is associated with varying degrees of toxæmia, although the extent of the membrane may be the same.

The toxin rapidly leaves the circulation for the tissues, so that the concentration in the blood stream is never very great. The avidity of toxin for living cells is of a very high order, and toxin taken up from the circulation quickly combines with tissues all over the body. The nature of the tissue-toxin combination is uncertain. Probably at first toxin is loosely bound; later it becomes firmly fixed, and when this occurs cannot be dissociated or neutralised by antitoxin. In highly susceptible patients this irreversible fixation of toxin occurs within a few hours of its liberation, and if the process is sufficiently intense, widespread or prolonged it results in the death of the patient. The toxin of diphtheria is capable of damaging all living tissues, but it has a particular affinity for heart muscle and nervous tissue. Although the fixation of toxin to these tissues occurs early in the disease, a latent period elapses before there is clinical or pathological evidence of specific damage to the heart and nervous system. In the case of the heart the specific effects do not appear until the second week; and the damage to the nervous system does not show itself until the third to the seventh week.

Apart from the presence of membrane, the macroscopic post-mortem appearances are not characteristic, but conform to those found in any acute toxæmia. Even these may be absent when death occurs in the late paralytic stages. Histologically, there is evidence of toxic degeneration in all organs, the most significant being found in the heart and nervous system, although changes in the reticulo-endothelial system, the lymphatic glands, the kidneys, suprarenals and liver are also important. In the heart there is evidence of a widespread toxic myocarditis—hyaline and fatty degeneration with some œdema, congestion and cellular infiltration. Both the cardiac muscle and the conducting mechanism are affected, although the relative involvement of these two structures varies. Later a reparative process sets in with muscle regeneration and sometimes interstitial fibrosis. In the

paralytic stages changes in the nerves of the heart can be detected.

In the nervous system degenerative changes appear in nerves and nerve cells. In the nerves the changes are those of a toxic peripheral neuritis: they disintegrate; the myelin sheaths lose their homogeneous character and are replaced by fatty globules. These changes are most marked in the nerves to eyes, palate, pharynx, larynx and heart, although a generalised peripheral neuritis sometimes occurs. Changes in cranial nuclei and in anterior horn cells have also been described. Although it is probable that the nervous system is affected by the toxin circulating in the blood stream, there is convincing evidence that most of the paralyses are the result of the transportation of toxin from the site of the membrane along lymphatic channels in the nerves to their centres in the medulla and spinal cord. It thus resembles the mode of spread of the toxin in tetanus and of the virus in poliomyelitis and hydrophobia, all of which spread directly from the local lesion to the nervous system.

Clinical and biochemical tests are sometimes employed to determine the degree of visceral damage in diphtheria. The fall in blood pressure, which is a striking feature of the second stage of the disease, has been attributed to action of toxin on the cardiovascular structures themselves, to damage to the suprarenals, and to involvement of the nervous centres. How much each of these contributes is uncertain. In the earlier stages of the disease there is clinical, electrocardiographic and histological evidence of damage to the heart—enough to account for most of the cardiovascular manifestations; later in the paralytic stage this is not so, and damage to the nervous centres is a more likely explanation.

Other evidences of disturbed metabolism in diphtheria are the diminished sugar tolerance, the diminished excretion of vitamin C (ascorbic acid) in the urine and the increase in bleeding and coagulation times.

The degree of abnormality in these biochemical processes corresponds with the intensity of the attack and tests for estimating them are sometimes used as ancillary to clinical methods for assessing the severity of cases of diphtheria.

Incubation period ranges from **two** to **four** days, with extreme limits of one to six days.

The clinical stages of the disease are three :—

(i) The initial stage, occupying the first week, during which the local lesion is present with general toxæmia of varying degree. According to the severity of the case this stage may

be followed by (ii) a stage of circulatory impairment during the second week; (iii) a stage of nervous complications, the most striking of which are paralyses appearing in the third to the seventh weeks.

The time at which these stages begin is not so exact as the above summary suggests. The severity and the duration of the manifestations in each stage are also very variable. Generally, the more severe the initial symptoms, the more quickly do the subsequent ones appear, the greater their severity and the longer they last. In the worst cases the initial manifestations may still be present when the cardiovascular involvement manifests itself on the seventh or eighth day. If the patient survives, the first of the paralyses appear in a few days. On the other hand, if the attack is mild the initial stage may be over in three or four days and the second and third stages may never appear. In the moderate cases there is considerable variability in the appearance of the subsequent manifestations. It commonly happens, for example, that the initial stage clears up in four or five days and no other clinical signs appear until the third or fourth week, when definite, but not dangerous, paralyses occur; the cardiovascular stage is either absent or so insignificant that the damage can only be detected electrocardiographically, if at all. Sometimes cases occur in which the cardiovascular manifestations give cause for anxiety but are not followed by paralyses. Lastly, cases occur in which cardiovascular and paralytic symptoms occur in a patient in whom the original manifestations were so mild that subsequent symptoms were not expected. In such cases the severity of the initial stage has usually been under-assessed. Despite these variations, the general rule is that subsequent manifestations depend upon the severity of the initial stage. Death may occur at any one of these three stages. In the first stage it is due to toxæmia and occurs at about the end of the first week. In the second stage it is due to cardiac failure and consistently occurs on the fifteenth or sixteenth day. In the third stage it results from respiratory failure, broncho-pneumonia or cardiac failure, and the critical time is the sixth week.

Clinical types of the disease: Classification.—A convenient clinical classification of diphtheria is based upon the anatomical distribution of the membrane, *e.g.*, nasal, tonsillar (faucial), pharyngeal, laryngeal diphtheria, etc. Since membrane tends to spread in the upper respiratory tract it is not unusual to find it involving more than one anatomical area. Unfortunately, a classification based on purely anatomical

considerations is defective as it does not necessarily indicate the degree of general disturbance and therefore the severity of the attack. A simple classification into mild, moderate and severe, based upon the general condition of the patient, is the most satisfactory, but is not precise enough for clinical record. Sometimes other terms are used to designate a prominent feature, such as toxic, hypertoxic, hæmorrhagic, œdematous, malignant.

The classification in Table XI is primarily anatomical, but consideration is given to the general toxæmia which accompanies each type, so that the disease can be reclassified into three simple types—mild, moderate and severe.

I. ANTERIOR NASAL DIPHTHERIA

This form of diphtheria is invariably mild. Constitutional disturbance and pyrexia are usually slight or absent. The chief sign is nasal discharge, which may be bilateral or unilateral. The discharge is thin and serous at first, and is frequently blood-stained ; later it becomes thicker and mucopurulent. Occasionally the bleeding is profuse enough to constitute a definite epistaxis. In a proportion of cases, if the discharge is wiped away, membrane is visible on the mucosa of the anterior nares as a whitish deposit most easily seen on the septum. The discharge sometimes excoriates the anterior nares and upper lip, but a more common cutaneous manifestation is the existence of small follicular spots or pustules on the face around the nose. In the mildest form of the disease (sometimes called diphtheritic rhinorrhœa) the condition is merely catarrhal : the discharge is not blood-stained, no membrane is present and general disturbance is absent. Anterior nasal diphtheria rapidly responds to antitoxin treatment : the discharge dries up and any general disturbance disappears in a few days. The diphtheritic nature of the condition is, however, frequently overlooked and specific treatment withheld. In such circumstances the discharge may continue for weeks, and some debility may supervene. Absorption of toxin is, however, slight, and cardiovascular manifestations and paralysis practically never occur. If a case, thought to be anterior nasal diphtheria, shows more than mild toxæmia, or if serious complications supervene, the probability is that the nasopharynx is, or has been, involved and the case more probably belongs to the pharyngeal type.

Anterior nasal diphtheria may, however, occur in combination with faucial, laryngeal or pharyngeal infections and

TABLE XI—CLINICAL FORMS OF DIPHTHERIA

Designation	Site Involved	Degree of Toxæmia	Clinical Severity
Anterior nasal .	Anterior nasal mucosa only	None or slight	Mild.
Laryngeal .	Larynx, with or without extension down to trachea and bronchi	Slight or moderate	Mild, moderate or severe.
Tonsillar (Faucial)	Tonsils	Slight or moderate	Mild or moderate.
Pharyngeal .	Tonsils with extension to one or more of the following : pillars, pharynx, palate, uvula, post-nasal mucosa and extensions.	Severe or very severe	Severe.
Non-respiratory	Sores on face, abraded surfaces, the genitals, conjunctiva, wounds, etc.	Very variable	Very variable.

Combinations of the above types increase the severity accordingly.

these take clinical precedence. Mitis strains are more frequently found in anterior nasal diphtheria than in any other form of the disease. When conveyed to others, the same form is *usually* produced in the new host. In a percentage of cases the bacilli persist in the nose after the clinical condition is cured (see Convalescent Carriers, p. 168).

Differential Diagnosis.

1. *Acute Coryza (Common Cold)*.—Anterior nasal diphtheria often begins like a common cold. In the latter, membrane does not form, epistaxis is rare, but slight conjunctivitis is common.
2. *Streptococcal Rhinitis*.—In scarlet fever rhinitis due to hæmolytic streptococci is not uncommon. Here again membrane does not form and epistaxis is rare ; but diphtheritic rhinorrhœa also occurs as a secondary infection in scarlet fever, and differentiation must depend upon the result of tests (see Diagnosis of Doubtful Cases).
3. *Foreign Body in the Nose*.—Children frequently insert foreign bodies, such as beads, into the nose, and such cases sometimes present a unilateral nasal discharge with or without epistaxis. The anterior nares should be examined in all cases as the detection of the foreign body (not always visible) or of membrane furnishes the diagnosis. Occasionally a foreign body and nasal diphtheria coexist.

II. TONSILLAR AND PHARYNGEAL DIPHTHERIA

The terms *faucial* and *pharyngeal* diphtheria are sometimes used as synonyms. Here, however, "pharyngeal" refers to a more extensive and more severe form than faucial. In *faucial* diphtheria the membrane is confined to the area between the pillars of the fauces, *i.e.*, mainly upon the tonsils ; hence it is sometimes called *tonsillar* diphtheria and this term is to be preferred. Once this area is passed the condition is *pharyngeal* diphtheria.

Clinical Features.—The onset of the disease may be abrupt, but it is more often insidious. Malaise, anorexia, nausea or vomiting, headache, pyrexia and sore throat—the usual initial symptoms of an upper respiratory tract infection—are common. But sore throat may be so inconspicuous that attention is not directed to the fauces. If the throat is not examined the diagnosis will be missed and delay in the administration of

specific treatment may have fatal consequences. Swelling of the neck from glandular enlargement is sometimes noticed and may indeed be the most prominent symptom.

It is in faucial and pharyngeal diphtheria that the three stages of the disease described above are typically present.

INITIAL STAGE.

Four local signs are of the utmost importance, and their presence and degree are valuable indications of clinical severity.

1. Extent, character and rapidity of spread of the *membrane*.
2. Presence of *œdema* in the fauces, uvula and pharynx.
3. *Fœtor* of the breath.
4. Presence of *adenitis and periadenitis*.

1. **Membrane.**—It is of the utmost importance to realise that at the beginning of the disease membrane is not present, although within twenty-four hours an extensive deposit may appear. This emphasises the need for watching patients with sore throat. In the mildest forms of the disease membrane *never* appears, the fauces being merely injected (catarrhal type); but such attacks are rare and occur only in patients with relatively high immunity; diagnosis cannot be made on clinical signs alone, and recourse must be had to accessory methods (see p. 158). Usually by the time the patient with diphtheria is examined, membrane has formed.

(i) *Appearance of Membrane.*—The membrane consists of a smooth patch which appears to be deposited on the mucosa, but if an attempt is made to scrape it off, it is found to be adherent. If forcibly removed a little bleeding results, but the underlying mucosa is not ulcerated and the membrane re-forms in twenty-four hours. If placed in water it sinks and does not disintegrate easily. Its colour varies: usually ivory-white or cream, it may be greyish, yellowish or greenish-white; or if there is any admixture with blood, dirty grey or even black. Membrane may be thin or thick; a heavy cast is usually evidence of severity. Old membrane is thick, opaque and sharply defined; young membrane is less clearly delineated, thin, glistening, slightly translucent, these qualities being best seen at the peripheral, spreading edge, particularly if this is present on the soft palate. Usually membrane presents itself as a single patch, *e.g.*, on each tonsil; occasionally more than one patch occurs in a particular situation, the tendency to spread and coalesce usually resulting in the formation of one large patch.

(ii) *Extent and distribution* vary considerably. In the

mildest cases of *tonsillar* diphtheria a small patch occupies part of one tonsil, and such unilateral distribution is very suggestive of diphtheria. Occasionally quite extensive membrane is limited to one side, but this is uncommon and care should be taken to exclude other diseases. In more marked cases both tonsils may be affected—sometimes equally on the two sides, sometimes more extensively on one side than the other. When membrane extends to the pillars of the fauces it can be seen on the *anterior* pillars, but is usually obscured if on the *posterior* ones. A small patch of membrane is sometimes seen on one or both margins of the uvula—the parts which are in contact with the tonsils when the mouth is closed. Sometimes the whole of the uvula is covered with membrane. But the presence of membrane on the visible parts of the uvula should always give rise to the suspicion that membrane may also be present on the posterior aspect not only of the uvula but also of the palate, *i.e.*, the condition is *pharyngeal* diphtheria.

When membrane is present beyond the tonsils the condition is *pharyngeal* diphtheria. This term is not quite satisfactory as membrane is frequently present on structures not strictly within the pharynx although the latter is the most important site affected.

The tonsils and pillars are usually involved and the membrane extends beyond them in one or more directions and on to the following structures, which are affected in varying degree :—

Posteriorly, the lateral pharyngeal and posterior pharyngeal walls may be involved : *pharyngeal* is a correct anatomical description of this type.

Anteriorly, membrane is often present on the uvula and soft palate. In the most severe cases the hard palate and even the lips, cheeks and tongue are involved. A more correct anatomical name for this type would be *pharyngo-palatal* or *pharyngo-buccal*.

Superiorly, the nasopharynx, including the adenoid pad, may be involved, and this may be combined with diphtheria of the nose—*pharyngo-nasal* diphtheria. This results in a profuse, watery, serosanguineous discharge associated with obstruction to nasal breathing, and is quite common in the severe forms of pharyngeal diphtheria.

Inferiorly, the larynx may be affected—combined *pharyngeal* and *laryngeal* diphtheria ; the membrane may also spread down the trachea and bronchial tree.

Thus membrane varies from a small patch on one tonsil to an extensive sheet over a large area of the upper respiratory

tract, *including parts which are not visible on ordinary examination of the fauces.* It is important to realise how large this area is, because pharyngeal diphtheria sometimes occurs in which the visible parts escape or are only slightly affected. In infants, for example, the *retronasal* space and the *adenoid pad* may be mainly or exclusively affected, or these may coexist with laryngeal diphtheria, so that extensive membrane may be present in situations which result in extreme danger to the infant, yet little or nothing can be seen on ordinary examination of the throat.

Occasionally membrane in pharyngeal diphtheria is very localised, *e.g.*, a small patch on one pillar or on the uvula; but the possibility of hidden membrane must always be in mind. In tonsillectomised patients membrane may be limited to the lymphoid tissue of the lateral pharyngeal wall, which hypertrophies to compensate for the loss of the tonsils.

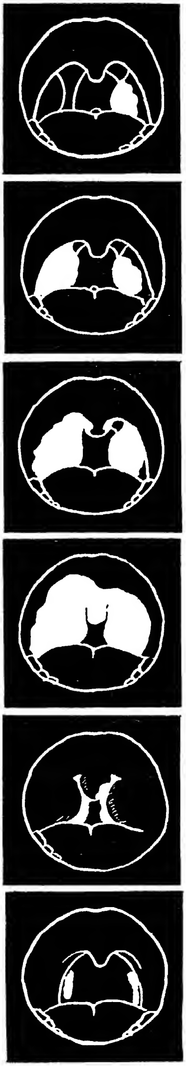
Generally, however, the extent of the membrane in pharyngeal diphtheria is greater than in tonsillar diphtheria, and as absorption of toxin is easier from the pharynx than from the tonsils, the majority of cases of severe toxic diphtheria fall within this group.

(iii) *Spread.*—It is a feature of diphtheria that the final area of membrane is usually greater than its initial extent. The rapidity with which spread occurs is evidence of severity. In the worst cases the appearance of the fauces and pharynx may be transformed in twelve to twenty-four hours—a small patch becoming a widespread membrane. Generally, however, the extension is slower. It continues for several days, until death supervenes or until the development of resistance or the administration of antitoxin arrests the process.

The response to antitoxin treatment is a valuable index of severity. A poor response or actual extension of the membrane is evidence of a severe attack (see Treatment).

Cases of diphtheria occur in which no spread occurs after the patch appears. They are usually mild.

2. **Congestion and Œdema.**—The appearance of the adjacent mucosa is informative. In the ordinary case it is practically normal, except for a narrow band of erythema adjacent to the spreading edge. This is a useful point in differential diagnosis. In severe cases, however, congestion and œdema occur. Swelling of the palate, pillars and uvula, combined with enlargement of the tonsils, may occlude the opening of the fauces and may obscure extensive membrane. Mixed infection with hæmolytic streptococci sometimes contributes to this appearance.



Tonsillar Diphtheria.—Mild: patch of membrane on the left tonsil.

Tonsillar Diphtheria.—Moderately severe: membrane on both tonsils, more extensive on the right than on the left.

Pharyngeal Diphtheria.—Membrane on both tonsils spreading, on the right, on to the pillars of the fauces; a little membrane on the margins of the uvula.

Pharyngeal Diphtheria.—Severe: extensive membrane on tonsils, pillars of fauces, palate and uvula; moderate œdema.

Pharyngeal Diphtheria.—Severe: considerable œdema of the fauces and uvula, almost obscuring membrane in the pharynx; the small patch on the left side of the uvula in itself suggests diphtheria.

Diphtheria in a tonsillectomised patient: two small patches of membrane on the lateral pharyngeal wall.

FIG. 12.—Appearance of the Fauces in Diphtheria.

3. **Fœtor.**—The odour of the breath is characteristic and cannot be described in words. It is pronounced in the worst cases and imperceptible in mild ones. Its detection depends upon the acuity of the observer's sense of smell and upon his experience.

4. **Adenitis and Periadenitis.**—Some degree of adenitis is common. In mild tonsillar cases the tonsillar glands draining the affected side or sides are slightly enlarged, just visible below the angle of the jaw and slightly tender. In the more severe cases the enlargement is greater. The most pronounced enlargement is encountered in pharyngeal diphtheria in which swelling of the neck is due not only to adenitis but to a swelling of the tissues of the neck around the glands which obscures their outline. This periadenitis is very suggestive of pharyngeal involvement, and in its most extreme form produces a swelling of the whole neck from the angle of the jaw to the clavicles (bull neck). Tenderness is not a marked feature and suppuration does not occur unless there is secondary infection with other organisms, *e.g.*, hæmolytic streptococcus. Periadenitis is a sign of severity.

Toxæmia.—Except in laryngeal diphtheria, where mechanical obstruction may occur, the local lesion of diphtheria is of importance in direct proportion to the amount of toxin produced there and absorbed into the circulation. The extent of membrane is a measure of toxin production or potential toxin production, but absorption depends upon the part of the respiratory tract affected. Thus although some degree of toxæmia is present in every case, it is trivial in anterior nasal, unimportant in pure laryngeal, mild or moderate in tonsillar and usually severe in pharyngeal diphtheria.

At the onset toxæmia causes headache, one or two attacks of vomiting, pallor, limpness, fatigue and a rapid pulse and slight albuminuria. Pyrexia is not a striking feature, *and no reliance must be placed upon it as a sign of severity* ; the most toxic cases of diphtheria are not infrequently apyrexial. As, however, there is no clear demarcation between the toxæmic manifestations of the first and second stages of diphtheria, these are considered together below.

STAGE OF CIRCULATORY IMPAIRMENT.

The features of this stage are the presence of toxæmia with evidence of particular involvement of the cardiovascular mechanism. In the mildest cases most or all the manifestations are lacking, but it is important to emphasise that even in the most severe and fatal cases one or more of the criteria

may be absent, so that consideration must be given to all of them in assessing the severity of the case.

The most significant features are :—

(i) *Muscular*.—Fatigue and limpness are common signs and may advance to prostration.

(ii) *Nervous*.—Lethargy or drowsiness may, in the most severe cases, give place to stupor and coma ; sometimes restlessness or even delirium occur, and are serious signs most commonly seen as the heart is failing.

(iii) *Circulatory*—(*a*) *Peripheral*.—Simple pallor is usual, but with impending failure of the circulation a waxy appearance, with or without a cyanotic tinge, may occur. Alterations in the rate, rhythm and tension of the pulse are frequent. The most common is simple tachycardia (110 to 140) associated with a soft compressible pulse. The fall in blood pressure is a special feature of the second stage and systolic pressures of 60 are not uncommon in severe cases. For some hours before death the pulse is often imperceptible and is associated with coldness of the extremities. Bradycardia, either simple or associated with conductive lesions, and irregularity of the pulse are less common. They usually occur in the second week, and are of serious significance. Hæmorrhages into the skin are seen only in very toxic cases which are almost always fatal. They are usually petechial, few in number and scattered over the body, but are most commonly seen on the swollen neck and around sites of therapeutic injection where they may form small extravasations. In such cases bleeding into the membrane and into the adjacent mucosa is usual and may result in considerable hæmorrhage from the mouth and nose. (A little bleeding at the time of separation of membrane is, however, not uncommon in ordinary attacks.)

(*b*) *Cardiac*.—Although as a rule there is a correspondence between the clinical and electro-cardiographic changes, not infrequently one or other may exhibit no gross abnormality. Clinical signs are seldom pronounced and minor degrees of cardiac involvement may be difficult or impossible to detect.

In the first week clinical and electro-cardiographic signs are frequently absent or insignificant ; yet death may take place in the first few days. This *early circulatory failure* of Schwentker and Noel is generally attributed to the sum of the toxic effects on *all* organs. It almost invariably occurs in severe toxic pharyngeal cases, most frequently due to gravis strains of the organism. Death is heralded by the rapid onset of prostration, extreme pallor, a rapid soft pulse, an extreme fall in the blood pressure and coldness of the extremities.

Begg (1937) considers that the degree of disturbance of carbohydrate metabolism (indicative of the general toxæmia) is a better prognostic sign at this stage than clinical and electro-cardiographic changes.

In the second week the clinical and electro-cardiographic changes are more pronounced. The most frequent clinical sign is a diminution in the intensity of the first sound at the apex which approximates to, and becomes weaker than, the second sound. In more severe cases reduplication or splitting of the sounds occurs. Gallop or triple rhythm is a common terminal event. Mason-Leete (1938) considers triple rhythm due to splitting of the first sound a more serious omen than that due to reduplication of the second.

A little dilatation of the heart with displacement of the softened apex beat downwards and to the left, and associated with a soft systolic murmur in the mitral area, occurs in cases of moderate severity. If heart failure supervenes, these changes are more pronounced (*vide infra*).

Alterations in rate and rhythm are best considered with the electro-cardiographic changes.

The electro-cardiographic abnormality falls into two groups :—

A. *Changes indicative of general* MYOCARDITIS.—The most common is an alteration of the ventricular complex (QRS) which tends to lose its sharp points at Q and S, producing a *slurring* of the lower limbs of the R wave. It is commonly associated with changes in the direction, amplitude or form of the T wave in significant leads. Sometimes low voltages (small amplitudes) of the ventricular complex in all three leads occur. Individually, these changes are not of serious import ; combinations indicate more severe myocarditis, but recovery is common.

Extra systoles and *nodal rhythm* are sometimes seen, but by themselves have little prognostic significance.

Tachycardia not of sinus origin, *e.g.*, *paroxysmal auricular* or *ventricular tachycardia*, is uncommon and is usually associated with a fatal issue. Ventricular fibrillation is a common terminal event.

B. *Changes indicative of* CONDUCTIVE *lesions*.—

(i) If the main bundle of His is involved, *complete heart block* occurs and results in dissociation of the auricular and ventricular rhythms with *bradycardia*. The latter is sometimes absent, and the existence of the block cannot even be suspected on clinical

grounds. The outlook is grave, but recovery occurs in a small percentage of cases, particularly in those

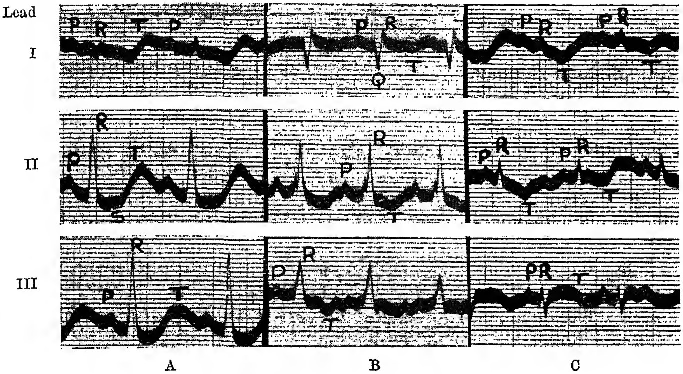


FIG. 13.—Degrees of Myocarditis.

A.—Slurring of the R wave and deep curved S in leads II and III and a biphasic T wave in lead I. Moderate myocarditis.
B.—The ascending limb of the R wave in lead II is splintered; there is slight intraventricular delay; the T wave is inverted in each lead. More severe myocarditis.
C.—The maximum voltage of the R wave in any lead is 0·5 millivolt. The T wave is inverted in leads I and II. Severe myocardial damage.

(*By courtesy of Dr N. D. Begg and the Editor of* THE LANCET.)

in whom the block is transient. Partial heart block (prolongation of the P—R interval and dropped beats) is rare in diphtheria.

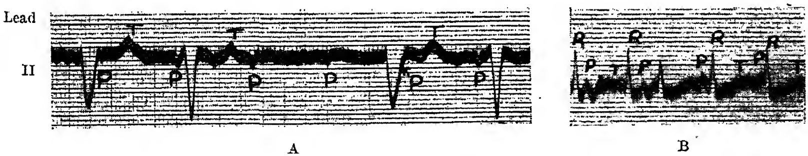


FIG. 14.—Complete Heart Block.

A.—The ventricular rate is slow (32); the auricular rate is 85; there is complete auriculo-ventricular dissociation; a ventricular extrasystole recurs regularly after each ventricular beat. Complete heart block with coupled beats.
B.—The ventricular rate is fast (135); the auricular rate is 100; the auricle and ventricle are beating independently and regularly. Complete heart block with fast ventricle.

(*By courtesy of Dr N. D. Begg and the Editor of* THE LANCET.)

(ii) If one or other of the two branches of the bundle is affected, *bundle-branch block* occurs. The R or S wave is widened and notched and the T wave is opposite in direction to the initial deflection of the

ventricular complex. The left branch is more frequently affected and the changes are evidence of serious damage to the heart.

Lead

I

II

III

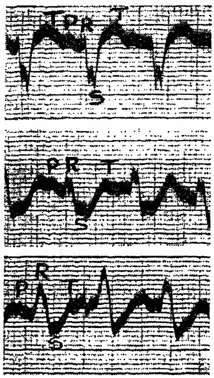


Fig. 15.—The wide-notched QRS complexes are directed upwards in lead III and downwards in lead I. The T wave in lead I is opposite in sign to the main initial deflection, but in lead III it is in the same direction. Right bundle-branch block.

(*By courtesy of Dr N. D. Begg and the Editor of* THE LANCET.)

(iii) *Intraventricular block* indicates involvement of the terminal part of the conducting mechanism, and is the least serious of the conductive lesions. QRS is widened and slurred or notched; the T wave is either upright, of low amplitude, or inverted.

Lead

II

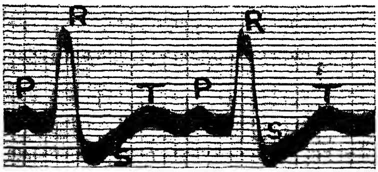


Fig. 16.—The QRS complex is wide (0·12 sec.), notched and directed upwards in each lead; the T wave is upright. Intraventricular block.

(*By courtesy of Dr N. D. Begg and the Editor of* THE LANCET.)

Death in diphtheria most commonly occurs in this second stage, and is the result of heart failure (*late circulatory failure*

of Schwentker and Noel). Some indication of impending failure is not infrequently given by three extracardiac signs :—

(i) *Vomiting*, which, if it appears at this stage, must be regarded as a *grave prognostic omen* ; it must be distinguished from vomiting due to serum disease, which may also occur at this time and which is not serious.

(ii) *Albuminuria* and *oliguria* ; the urine should be measured and tested daily ; anuria is always associated with a fatal issue.

(iii) *Restlessness*.

Alterations in the character of the heart sounds, dilatation of the heart and alterations in rate, particularly bradycardia or gallop rhythm appear. Præcordial and abdominal pain, with enlargement and tenderness of the liver, may be present. The blood pressure falls, the pulse becomes imperceptible, the extremities cold and death supervenes.

If recovery occurs the cardiac condition clears up entirely. Clinical and electro-cardiographic examinations during convalescence are almost invariably negative. Nevertheless, exercise-tolerance is diminished for many months if the heart has been seriously affected and strenuous exercise should be avoided. Buller and Levine (1930) suggest that diphtheria predisposes to earlier sclerosis in later life.

STAGE OF PARALYSIS

The features of the paralyses of diphtheria are :—

(i) The order in which they appear ;
(ii) The latent period which precedes their onset, and the interval between the paralyses themselves ;
(iii) The almost complete escape of the sensory nervous system, *i.e.*, the paralyses are motor.
(iv) The absence of permanent damage.

The order in which the chief paralyses usually occur and the stage of the illness at which they commonly appear are :—

PARALYSES	TIME OF ONSET
1. Palate	Third week (fourteenth to twenty-first day).
2. Eyes	Fifth week (twenty-eighth to thirty-fifth day—variable).
3. Heart, pharynx, larynx, diaphragm.	Seventh week (forty-second to forty-ninth day).
4. Peripheral neuritis of limbs.	Seventh to tenth week (forty-second to seventieth day).

Paralyses do not invariably occur; mild cases almost always escape or exhibit a paresis only. The less severe the disease, the less likely are the later and severer types (3 and 4 above) to occur. In milder cases the time of onset tends to be later. Paralysis and paresis are usually bilateral; sometimes one side is more markedly affected than the other; occasionally they are unilateral.

Paralysis of the soft palate is the commonest and earliest. If the palate escapes subsequent paralyses are extremely unlikely, although occasionally the eyes are affected without the palate having been involved. The *signs* of complete paralysis of the palate are—

(*a*) *Immobility*: detected by asking the patient to say "Ah": in the normal person the palate arches upwards; this movement is absent if the palate is paralysed.

(*b*) A *nasal* quality to the voice: detected by asking the patient to say "plum pudding" or "pretty Polly kiss the cook."

(*c*) *Regurgitation* through the nose of fluids taken by mouth.

(*b*) and (*c*) are due to the immobility of the palate preventing the closure of the mouth from the nose, necessary for swallowing and for the phonation of consonants such as *p* and *b* and of vowels such as *a* and *o*.

Paresis, or weakness, is even commoner than *paralysis*, but may be overlooked as one or more of the above signs may be absent. *Unilateral* paralysis is sometimes seen, the weak side being the one on which the membrane was more extensive.

Paresis of the palate may be so transient that it can be detected for a few hours only; generally it lasts for one to two weeks and then disappears entirely. In the mildest cases the signs can only be detected, or are worse in the evening, when the patient is tired. In the worst cases *precocious palatal paralysis* may appear in the first week of the disease.

Ocular palsies are usually *intrinsic*, the most common being paralysis of *accommodation*. If this occurs alone, there are *no objective signs* and diagnosis depends upon the patient's complaint of blurred vision. It is therefore frequently missed, particularly in children too young to complain. In more extensive involvement, the size of the pupils and their reaction to accommodation and light may be altered. Less commonly the *extrinsic* muscles are affected, causing squint. Ptosis is rare.

A paresis or paralysis of the *face* occasionally appears at this time. It usually affects the lower part and may be unilateral or bilateral.

Paralyses of the Heart, Pharynx, Larynx and Diaphragm usually appear about the same time, and frequently two or more are present together. They are the most serious of the paralyses and are responsible, either directly or indirectly, for the deaths which occur at this time.

The earliest sign of involvement of the nervous control of the *heart* is tachycardia, frequently followed by extra systoles and sometimes by gross irregularity. Dilatation may appear. Death from heart failure is uncommon, but cases of sudden death have not infrequently occurred in patients apparently convalescent following some trivial effort, such as sitting up in bed.

The *pharynx* is concerned with the soft palate in shutting off the oropharynx from the nasopharynx, so that when paralysed a nasal voice and regurgitation of fluids occur. In addition, deglutition is impaired and large quantities of mucus accumulate in the pharynx. If allowed to remain, mucus enters the respiratory tract, stimulates a reflex cough and may cause a fatal aspiration-broncho-pneumonia. Since swallowing is impossible, the patient rapidly loses flesh and some form of artificial feeding is necessary.

The commonest manifestations of nervous involvement of the *larynx* are aphonia and a hollow " paralytic " cough.

In paralysis of the *diaphragm* respiratory difficulty occurs. Thoracic movements are laboured from overaction of the intercostals and accessory muscles of respiration. The upper abdominal wall, instead of rising with inspiration, is either immobile or falls in. If the intercostals are also involved dyspnœa is increased. Unless assistance is provided by some form of artificial respiration (*e.g.*, by Drinker respirator) respiratory failure or secondary broncho-pneumonia may cause death.

All these paralyses suggest involvement of the bulbar centres, and when they occur together it is sometimes difficult to assess the part which each plays. If the patient is going to recover, improvement appears in a week or fortnight, and is usually fairly rapid. Permanent paralyses never occur.

A widespread *peripheral neuritis*, involving particularly the extremities, is a rare complication which appears so late that, not infrequently, the patient has been discharged as recovered. It results in wasting and weakness of the muscles of the extremities, with loss of deep jerks. Sensory changes are absent or insignificant. Recovery is the rule, but is slow.

An *ataxic gait* and loss of *deep jerks* are common events in severe diphtheria, and convalescence is often prolonged whilst the patient learns to walk again.

Of different pathogenesis, viz., a vascular lesion, is the rare *hemiplegia*, which almost invariably leaves some permanent disability in the two-thirds who recover.

Differential Diagnosis of Faucial and Pharyngeal Diphtheria.—When there is doubt about the diagnosis, the Schick test and swabbing for *C. diphtheriæ* are of considerable assistance and should always be employed (*vide infra*). These tests, however, take time and the student must be familiar with the *clinical* differentiation.

1. ACUTE TONSILLITIS.—All forms of acute tonsillitis may be confused with diphtheria, but the membranous and ulceromembranous types are most likely to cause difficulty. Generally, sore throat is a more constant and pronounced symptom, pyrexia is greater and congestion of the fauces more marked than in diphtheria. The tongue and the buccal mucosa are frequently of considerable assistance in diagnosis.

(*a*) *Acute membranous tonsillitis* is most commonly due to hæmolytic streptococci, but other organisms such as pneumococci and staphylococci are occasionally responsible. As a rule the deposit is confined to the tonsils ; usually, but not invariably, it can be easily detached without causing bleeding ; the material of which it is constituted is softer and more pultaceous and disintegrates more easily in water than diphtheritic membrane. A *very* white deposit or membrane is usually not diphtheritic ; on the other hand, grey or greyish-black membrane is almost invariably diphtheritic. In hæmolytic streptococcal conditions, including scarlet fever, the appearance of the tongue, with or without the presence of the rash, is often typical.

(*b*) *Ulceromembranous Tonsillitis.*—Although certain severe types of diphtheria, particularly those associated with secondary infections, may exhibit visible erosion of the mucosa, in general the presence of ulceration is against the diagnosis of diphtheria. Ulceromembranous tonsillitis is not uncommonly unilateral, and if the ulceration is not deep, may be largely obscured by the deposit or exudate.

(i) *Vincent's angina* is the commonest ulceromembranous lesion encountered. It is not

necessarily confined to the tonsil. Gingivitis, usually non-ulcerative, is a common accompaniment. Toxæmia is not a common feature. Fœtor of the breath is different from and much more unpleasant than that of diphtheria. Many of the patients are not children. The presence of the spirillum and the fusiform bacillus in a direct smear confirms the diagnosis (*vide* Chapter XIV).

(ii) *Severe hæmolytic streptococcal* infection of the fauces, including septic types of scarlet fever, may cause ulceromembranous lesions. The tongue and the congestion of the fauces are suggestive and the presence of hæmolytic streptococci in large numbers confirms the diagnosis which, in scarlet fever, is aided by the presence of the rash.

(iii) Rarer causes: *Agranulocytic angina*, most common in middle-aged women who have been taking amidopyrine or drugs related to the sulphonamides, is diagnosed by blood examination which reveals leucopenia, and relative and absolute granulocytopenia. In the worst cases there may be no neutrophils at all.

In *acute leukæmia* attention may be directed in the first instance to oral and faucial symptoms associated with pyrexia. Hæmorrhage from the gums and elsewhere, purpura and the blood picture are the chief differentiating features. Enlargement of the spleen, liver and lymphatic glands is not marked, but is usually present.

Although cervical adenitis is a usual accompaniment of ulceromembranous tonsillitis, the presence of considerable periadenitis is strongly suggestive of diphtheria.

(*c*) *Acute catarrhal, follicular* and *herpetic* tonsillitis are clinically distinctive, but types of diphtheria are described resembling them. The vast majority are not true diphtheria but examples of carriers suffering from angina and who have been swabbed for diphtheria bacilli and found positive, without investigation of their state of immunity (Schick test) (*vide infra*).

(*d*) *Tonsillomycosis* usually occurs in adults, either primarily or as a complication of, *e.g.*, enteric fever. It is due to a fungus of the monilia type, resembling the organism responsible for thrush. Patches and spots of soft deposit occur on the tonsils, soft palate, uvula and often the buccal mucosa. The mouth is usually dirty. Ordinary *thrush* producing dead white patches of haphazard distribution, but mainly affecting the buccal mucosa of infants, should not be confused with diphtheria.

2. POST-TONSILLECTOMY SLOUGHS.—The appearance of the fauces after tonsillectomy may closely resemble diphtheria, particularly if the deposit on the site of the operation extends beyond the fossæ to the pillars of the fauces. There is no tendency for the lesions to spread. Difficulty may arise in carriers unless both Schick testing and swabbing are carried out (*vide infra*). Occasionally diphtheria is precipitated by the operation.

3. QUINSY, is much commoner in adults than in children. It is usually unilateral. Sometimes a deposit is present on the tonsil. There is considerable swelling and injection in the peritonsillar area, and the local glands are enlarged and definitely tender. Distinctive features are the severe sore throat, dysphagia and trismus, all of which are against a diagnosis of diphtheria. Fluctuation in the peritonsillar tissue may be present. Hæmolytic streptococci are usually responsible and can be detected on swabbing.

4. SYPHILIS.—Chancre of the tonsil occurs in adults. It produces an indurated ulcer from which *T. pallidum* can be isolated and seen with a dark ground microscope. In secondary syphilis serpiginous " snail track " ulcers and mucous patches may be confused with diphtheria. The cutaneous manifestations are either present or soon appear, and there is general slight adenitis, most suggestive if the supratrochlear glands are affected. The Wassermann reaction is positive at this stage.

5. MUMPS.—One of the gravest mistakes made in the practice of infectious diseases is to confuse the periadenitis of diphtheria with mumps, as specific antitoxin is withheld from the type of case which urgently needs it if life is to be saved. It usually means that the fauces have not been examined. In mumps the swelling extends from the angle of the jaw on to the face as far as the zygoma, and posteriorly it fills up the depression between the angle of the jaw and the mastoid process. The orifices of Stensen's duct are injected.

In diphtheria the periadenitis is mainly in the neck, although it may extend over the angle of the jaw, *i.e.*, it is lower than in mumps. Cases of diphtheria with periadenitis are usually toxic and membrane can usually, but not invariably, be seen on examination of the fauces.

6. SCARLET FEVER.—The tonsillitis or tonsillo-pharyngitis of scarlet fever may be membranous or, in septic types, ulcero-membranous. It is identified with the hæmolytic streptococcal tonsillitis described above. The presence of the rash is an additional distinguishing feature.

7. NEUROLOGICAL CONDITIONS.—If the primary stage of diphtheria has been overlooked, or if its diphtheritic nature has not been appreciated, difficulty in diagnosis may arise when the paralytic stage appears. The paralyses of diphtheria occur in apyrexial subjects; the structures chiefly affected are the intrinsic muscles of the eye and those muscles with centres in the medulla; they appear in a certain order; pain is absent; the sphincters are not involved; and signs of meningitis do not occur. These features and the examination of the cerebrospinal fluid are usually sufficient to differentiate such conditions as the bulbar type of *poliomyelitis*, *epidemic encephalitis*, *tuberculous meningitis*, *syphilis of* the *nervous system*, particularly *tabes*, and *peripheral neuritis* due to diabetes, lead and alcoholism. *Post-serum paralysis* is most likely to be confused with the peripheral neuritis of diphtheria. The condition is a peripheral neuritis which appears rarely after the administration of the serum. It is usually preceded by pain. It may be widespread or localised, the brachial plexus and the muscles of the shoulder girdle being commonly involved. It produces flaccid paresis or paralysis with alteration in reflexes and disturbances of sensation, subjective and objective. Electrical reactions are diminished, but reaction of degeneration is rare. Recovery is the rule, but is slow (*e.g.*, two to nine months). Diagnosis is difficult except when serum has been administered prophylactically or when a retrospective diagnosis of diphtheria can be excluded.

8. RETROPHARYNGEAL ABSCESS is the other common condition which may cause a nasal voice and regurgitation of fluids. A palpable, often visible, swelling of the lateral or posterior pharyngeal wall is present.

III. LARYNGEAL DIPHTHERIA

Laryngeal diphtheria occurs most commonly in children between the ages of twelve months and five years. The

younger the child the smaller the glottis and the more dangerous is the disease likely to be. It may be "primary"—the larynx alone being affected, but more commonly it is "secondary" to faucial or post-nasal diphtheria.

The clinical picture is of an *acute laryngitis* in which signs of *respiratory obstruction* are relatively prominent. The chief symptoms of *any* acute laryngitis are pyrexia, cough and changes in the voice and cry—at first huskiness or hoarseness, later aphonia. In addition there may be symptoms of obstruction due to congestion, muscular spasm and, in *diphtheria*, to the presence of membrane. The first sign of obstruction, and sometimes the only sign in laryngeal diphtheria, is a harsh, rather barking quality to the cough—*croupy cough* or *stridulous cough*. The cry has a similar quality. When obstruction is more marked breathing becomes noisy (*stridor*, or stridulous breathing—most marked during inspiration). With increasing obstruction there occurs during *inspiration* overaction of the respiratory muscles with *recession* of the soft parts of the chest and excessive descent of the larynx. Lastly, when obstruction interferes with aeration, a variable degree of *cyanosis* and *restlessness* appear. Thus *dyspnœa is mainly inspiratory*, and the chief abnormality during expiration is the *croupy cough and cry*. Because of the ease with which reflex spasm can be excited in a child, the symptoms are aggravated or provoked by emotions such as fear or crying or examination.

The onset in laryngeal diphtheria is usually *gradual*. For the first twelve to twenty-four hours dyspnœa is *not* prominent, but when it appears it takes two forms :—

(*a*) An underlying *steadily progressive* dyspnœa of varying degree, which may advance slowly or with disconcerting rapidity ;

(*b*) Superimposed *exacerbations* or *paroxysms* in which the respiratory difficulty may suddenly become dangerous. Cases therefore fall into *three grades* of severity :—

In the mildest cases obstruction is trivial and no paroxysms of dyspnœa occur. The common symptoms are a croupy cough, a husky voice—which may progress to aphonia—and pyrexia. Slight stridor and recession may also appear. The condition may remain thus or advance to the next stage in which paroxysms of dyspnœa and restlessness occur, lasting from a few minutes to an hour or more and giving rise to temporary anxiety. They may be provoked by emotion or appear spontaneously, and often awaken the child during the night. When they subside, the patient, a little exhausted, may fall asleep

again, but in the intervals there is never complete freedom from symptoms. In the most severe cases, which are seen only in young children, the patient passes gradually or suddenly into a state of continuous and severe respiratory difficulty and requires immediate relief of the obstruction, usually by some operative measure, if life is to be saved. The aphonic child with the croupy cough struggles for air. The chest exhibits violent respiratory movements, but the ingress of air is inadequate, so that during inspiration there is loud stridor, marked descent of the larynx, deep recession of the suprasternal fossæ, the supraclavicular spaces and the epigastrium, sucking in of the intercostal spaces and even of the chest wall. Lividity of the lips and finger tips advances to cyanosis, the pulse is rapid and possibly irregular, and the forehead covered with perspiration. If this stage is prolonged, or an exacerbation occurs, restlessness gives place to prostration. The violent struggles quickly cease, the respiratory movements rapidly become feebler, the colour slatey-blue, the pulse thin and thready, stupor or unconsciousness supervenes, quickly followed by death. Alternatively, a *convulsion* may precede death.

This severe type of dyspnœa may supervene after antitoxin treatment has been instituted. Indeed, during the separation of membrane a partially detached piece may suddenly produce a serious exacerbation of the obstruction in a child regarded as having a moderate attack.

In the worst cases of laryngeal diphtheria some extension down the trachea or bronchi is common—combined laryngeal and *tracheo-bronchial* diphtheria. The whole bronchial system may be lined by membrane and the finer bronchioles partially or completely obstructed by membrane and mucopurulent exudate, and air entry to the lungs considerably diminished. A tree-like cast may be expelled from the tracheotomy wound, or be found at autopsy. Such cases are frequently complicated by a fatal form of *broncho-pneumonia* of diphtheritic origin.

Diagnosis and Differential Diagnosis of Laryngeal Diphtheria.—Laryngeal diphtheria is often associated with involvement of the nose, fauces and pharynx. Careful examination of these situations is imperative as lesions are often small. If they are present the diagnosis is plain. A laryngitis with changes in the voice and cough, progressive dyspnœa and asphyxiating paroxysms is due to diphtheria in 90 per cent. of cases.

Direct laryngoscopy, a valuable aid to diagnosis, reveals injected and swollen mucosa, usually with excessive mucous secretion. Membrane can sometimes, but not always, be seen

on the vocal cords and epiglottis. Aspiration of the mucus may be necessary before the membrane can be seen. A direct swab of the larynx for *C. diphtheriæ* is more likely to be positive than swabs taken of the nose and throat.

The following conditions require to be differentiated :—

ACUTE LARYNGITIS.—The important difference between laryngeal diphtheria and other acute laryngitides is the presence of membrane in the former, which increases obstructive signs. Owing to the small lumen of the larynx of the child and the ease with which reflex spasm can be excited, *any* acute laryngitis may be associated with obstructive symptoms ; but children exhibit considerable variation in the relative degree of catarrhal and obstructive signs. In some the catarrh is prominent and obstruction trivial or absent ; in others nocturnal attacks of stridor and dyspnœa are pronounced and the catarrhal symptoms so mild as scarcely to attract attention ; in a third group pronounced catarrhal and obstructive signs coexist, as occur in laryngeal diphtheria.

Acute laryngitis may therefore be divided into :—

(i) *Acute catarrhal laryngitis*, in which *catarrhal* signs are pronounced. It may complicate the common cold, acute tonsillitis, acute bronchitis, measles and, rarely, other infectious diseases.

(ii) *Catarrhal spasm of the larynx*, in which *obstructive* signs are dominant. Various other names applied to this syndrome are *laryngitis stridulosa* (not to be confused with *laryngismus stridulus*), *spasmodic laryngitis*, *pseudo croup*, *catarrhal croup*, *spasmodic croup*.

Special mention must be made of the acute laryngitis which may appear in measles during the pre-eruptive, *i.e.*, Koplik's spots, stage. This is a catarrhal laryngitis in which obstructive symptoms and bouts of dyspnœa may cause anxiety. At this stage of the disease it is almost invariably non-diphtheritic, although a similar syndrome, occurring later in the disease, is usually due to a secondary diphtheritic infection.

It will be obvious that there is no fundamental difference between these types of acute laryngitis. Clinical diagnosis rests upon the dominance of certain symptoms. Since life is at stake, every case must be treated as diphtheritic until proved not to be so.

The following *laryngeal* conditions require to be differentiated : *acute catarrhal laryngitis, catarrhal spasm of the larynx, laryngismus stridulus, congenital laryngeal stridor,*

papilloma of the larynx, acute œdema of the glottis and *foreign bodies in the larynx*. The chief points of distinction are given in Table XII. In *whooping-cough* there is no alteration in the voice or cry, and the attacks consist in paroxysms of coughing followed by an inspiratory whoop.

Pharyngeal, bronchial and *pulmonary causes* of stridulous breathing or dyspnœa require to be differentiated. In *retro-pharyngeal abscess* there is a palpable, often visible, soft swelling of the lateral or posterior pharyngeal wall, sometimes a nasal cry, and regurgitation through the nose of fluids taken by mouth. *Enlargement of the thymus* or *tracheo-bronchial glands* may be detected by radiology ; neither is sudden in onset. In *asthma* dyspnœa is mainly expiratory and respirations are wheezy and prolonged. In *broncho-pneumonia* respirations are rapid, shallow and sometimes inverted. Clinical signs in the chest may be difficult to detect (see Chapter VI). Radiology is of assistance. The association of tracheo-bronchial diphtheria with broncho-pneumonia is mentioned above. Obstructions below the glottis are not associated with excessive descent of the larynx.

IV. NON-RESPIRATORY DIPHTHERIA

These types are not common and lack characteristic features. They therefore escape early detection and treatment and are liable to become progressive or chronic. Usually the diphtheritic infection is superimposed upon some underlying non-diphtheritic condition, such as otitis media, sores on the face, paronychia, abraded surfaces, wounds, the genitals, the lesions of chicken pox (as in certain types of *varicella gangrenosa* (*q.v.*)). An indolent membrane is usually, but not invariably, present on the surface of the lesions. Commonly, the diphtheritic infection is due to autoinoculation from the respiratory tract, particularly the nose, where the disease may also escape detection. Paralyses similar to those occurring in respiratory types are occasionally seen, *e.g.*, paralysis of the palate or eyes ; but in most such cases a focus in the respiratory tract has gone undetected. Special mention must be made of *conjunctival* diphtheria. It may be unilateral or bilateral. Conjunctival injection and discharge, chemosis and swelling of the lids are present. A thin membrane can frequently be seen on the palpebral conjunctiva. Its early recognition is important because, if adequate treatment is delayed, rapid and complete destruction of the globe may result from extension of the membrane and resulting panophthalmitis.

True *aural* diphtheria is rare; most cases called aural diphtheria are examples of otitis media secondarily infected with *C. diphtheriæ* from the nasopharynx. Many patients are Schick-negative carriers. Organisms resembling *C. diphtheriæ* recovered from the ear should be fully investigated as some are diphtheroids.

Toxæmia in non-respiratory diphtheria is variable, but is usually slight, although delay in the diagnosis may result in general symptoms. Deaths rarely occur.

V. HYPERTOXIC, MALIGNANT AND HÆMORRHAGIC DIPHTHERIA

These terms are applied to a particularly severe and fatal form of diphtheria, usually pharyngeal, with overwhelming toxæmia. The hypertoxic features may manifest themselves from the onset, or they may develop in less severe pharyngeal types because of delay in the administration of antitoxin. *Gravis*, and, less frequently, *intermedius* types of *C. diphtheriæ* are usually responsible. In about half the cases other organisms, *e.g.*, hæmolytic streptococci, are associated with *C. diphtheriæ*. The clinical features differ only in degree from those described under pharyngeal diphtheria. Membrane is usually extensive; the fauces and pharynx are œdematous and red; fœtor is marked; "bull neck" is usual; a profuse, thin mucopurulent or sanious discharge is common; nasal obstruction results in mouth breathing and dysphagia is intense. The membrane is cream, grey or black, spreads rapidly, is firmly adherent, and there may be subjacent ulceration of the mucosa. The most striking feature is the profound toxæmia and rapid decline in the patient's condition; prostration, pallor, drowsiness or restlessness are rapidly followed by signs of cardiac failure. Hæmorrhages into the local lesion and the skin are common and such patients almost invariably die. The fatality rate among non-hæmorrhagic cases is frequently as high as 50 per cent. They are said to respond badly to antitoxin, but this is in part due to the fact that, by the time they are seen, it is too late for antitoxin to be of any avail.

THE DIAGNOSIS OF DOUBTFUL CASES OF DIPHTHERIA

When signs are insufficient to establish a diagnosis on clinical grounds alone, additional evidence can be obtained by carrying out tests :—

1. *Schick Test (vide infra).*—At the beginning of an attack of diphtheria the Schick test is usually positive. If the attack is such that antitoxin must be given *at once*, this test is not applicable as antitoxin inevitably renders it negative. If, however, the nature of the attack is such that it would not be dangerous to withhold antitoxin for *six hours*, the test can be used, as antitoxin administered after this time will not prevent a positive response from appearing. The test is *not* a test for the *disease* diphtheria ; it merely indicates susceptibility or immunity. A negative response at the beginning of the illness is strong presumptive evidence that the patient is immune and therefore not suffering from diphtheria ; but a positive response is *not* proof that the patient *is* suffering from the disease. In diphtheria, a positive reading tends to appear early—often as soon as twelve hours after the test.

In rare instances Schick-negative subjects develop diphtheria. Attacks are usually mild and *gravis* strains are most commonly responsible.

2. *Swabbing for C. diphtheriæ.*—The causal organism can usually, but not invariably, be isolated from the local lesion. In respiratory types of the disease, swabs should be taken from both nose and throat. A good view of the local lesion, *e.g.*, on fauces or pharynx, must be obtained ; in laryngeal cases laryngoscopy is necessary, or swabbing through a tracheotomy wound. No antiseptic gargle or paint should have been recently used. The swab must come in direct contact with the local lesion, and, by rotating the swab and using gentle force, some membrane should be removed from the periphery of the patch.

The swab may be used for making a *direct smear*, which can be examined at once, or it may be inoculated on a suitable medium (usually Loeffler's) for *cultivation* of the organism. The percentage of positive results obtainable from direct smear is not high, but a positive finding provides immediate evidence. Whether a direct smear is made or not, every swab should be cultivated. The medium should be inoculated as soon as possible, since delay diminishes the number of positive findings. The result of the culture is usually available in eighteen to twenty-four hours.

Solé swabs and their modifications contain a medium incorporated in the swab. It is claimed that results are available in about four hours if necessary.

Another rapid method advocated consists in rubbing a swab dipped into a 2 per cent. solution of potassium tellurate upon the suspected exudate *in situ* ; blackening occurs within

five to ten minutes if the exudate contains diphtheria bacilli, but unfortunately an unpleasant odour of garlic is produced, and, moreover, blackening occurs with other organisms.

The recovery of organisms with the morphological appearance of *C. diphtheriæ* is *not* evidence of the *disease*. The organism may be non-virulent or a diphtheroid ; if virulent, the patient may be a carrier. But their presence in a patient with *clinical signs suggestive of diphtheria* is usually sufficient *confirmation* of the diagnosis. In the absence of clinical signs, or where the appearances are grossly atypical, *virulence tests* must be performed and the state of immunity ascertained by the Schick test. The complete identification of *virulent C. diphtheriæ* takes five to seven days, but with few exceptions *gravis* and *intermedius* are virulent.

3. *Therapeutic Test.*—The *local* lesion responds to treatment with antitoxin if *an adequate dose by an adequate route has been given.* In twelve to twenty-four hours the membrane ceases to spread, and within three or four days disintegrates or separates, although in severe cases it may persist longer. A local condition which fails to respond in this way is probably not diphtheritic.

Procedure for Investigating and Treating Doubtful Cases.—When first seen, doubtful cases should be divided into :—

1. Those in whom delay in the administration of antitoxin would be dangerous if the diagnosis of diphtheria is ultimately confirmed : such patients must be given antitoxin *immediately* and swabs taken to confirm the diagnosis.
2. Those in whom a delay of *six hours* would not be dangerous : the Schick test should be performed and swabs taken ; six hours later antitoxin should be given.
3. Those in whom a delay of a *day or more* would not be dangerous : the Schick test should be performed and swabs taken and the administration of antitoxin deferred until the results are known.

This division obviously depends upon the clinical experience of the observer. *When in doubt give antitoxin.* It should be noted that *in no case is reliance to be placed upon the swab alone* as the information is sometimes misleading. Every suspected case, when first seen, must either *receive antitoxin and be swabbed* or must be *Schick tested and swabbed.*

The interpretation to be placed upon the results of these

tests is given in Table XIII. They apply only to patients who are ill and suspected to be suffering from diphtheria :—

TABLE XIII

INTERPRETATION OF RESULTS OF TESTS IN DOUBTFUL CASES OF DIPHTHERIA

Result of Schick Test	Result of Culture	Inference
Positive	Positive	Diphtheria.
Positive	Negative	Susceptible, but no diphtheritic infection. (Repeat swab to confirm.)
Negative	Positive	Immune. Culture to be typed and/or tested for virulence ; if virulent = diphtheria carrier. (Assume *gravis* and *intermedius* virulent.)
Negative	Negative	Immune ; no diphtheritic infection.

TREATMENT

1. **Nursing.** — *Immediately* diphtheria is diagnosed the nursing measures for severe toxæmia described in Chapter X, p. 79, should be instituted. In mild cases one flat pillow may be provided ; in all others the patient should be kept flat unless considerable discomfort results. Thereafter progress depends upon the severity of the attack and the presence of cardiac manifestations or paralyses. In a moderate attack an extra pillow is allowed each week. Four weeks after admission the patient is allowed to sit up in bed, read and feed himself ; then, to lie on a couch or sit in a chair ; later, he is permitted to walk, but if ataxic, re-education in walking is necessary. Increasing liberty of movement **must be gradual,** and if cardiac or nervous complications appear the patient must be put back, either flat or on one pillow.

After moderate attacks, patients are physically fit for

discharge in six or seven weeks. After mild attacks, *e.g.*, of anterior nasal diphtheria, they can be discharged earlier, *e.g.*, in four weeks; but it is important to be sure that there has been no retronasal membrane as such cases are *never* mild. In severe attacks with cardiac manifestations, the patient may be kept flat for three, four or more weeks, and if subsequent progress is interrupted by paralyses—as is common in such cases—stay in bed for eight or nine weeks may be necessary, making the total duration of treatment three months.

2. **Antitoxin.**—Toxin is distributed throughout the body, but is not uniformly accessible to antitoxin. There is, *firstly*, free circulating toxin, very small in amount, which is readily neutralised by antitoxin. *Secondly*, there is loosely bound toxin which has entered into the early stage of combination with the tissues, and probably can be influenced by antitoxin. *Lastly*, there is toxin in the final stage of *firm combination* with the tissues which is *entirely uninfluenced* by antitoxin. Since the last stage of the tissue-toxin combination is so firm as to be beyond the influence of antitoxin, it is of vital importance to bring antitoxin into action at the *earliest possible moment.* It is possible to save the patient if a lethal dose of toxin has not yet entered into firm combination at the time antitoxin is administered. In any individual case it is impossible to make an accurate estimate of the amount of toxin which has been produced, absorbed and fixed; but it is certain that in cases of severity the lethal dose is reached rapidly. The effectiveness of serum therapy, therefore, depends upon its *earliest possible employment*. The evidence is overwhelming that by far the most important single factor in the success of treatment with antitoxin is the *time factor*. "Every hour, every minute of delay—and this is not a figure of speech—is damaging. If the amount of toxin is near the lethal dose, life itself is at stake" (Schick). In less severe cases the early administration of antitoxin reduces the incidence of complications and in so doing causes the disease to run a milder and shorter course.

The object being to secure an effective concentration of antitoxin in the blood with the least possible delay, the route chosen for the administration is therefore of vital importance (see p. 163). Although, on account of rapidity of action, the intravenous is the ideal route, not all cases of diphtheria necessitate its use. On the one hand, the mild character of the attack, and on the other the possibility of shock and the difficulty of administration to very young and restless children, especially those with collapsed veins, limit its

application. Where speedy absorption is less urgent, the route of choice is the intramuscular. A single dose of antitoxin is far more efficacious than the same amount in divided doses. With a single dose a higher and earlier concentration of antitoxin in the blood is attained. Further, if the severity of the case has been properly assessed and an adequate amount of antitoxin given by a suitable route, the quantity persisting in the blood after a single injection should be sufficient to continue beneficial effects until the active phase of the disease has passed. If, from the course of the disease, it is obvious that the first dose was insufficient, the severity of the case has not been properly assessed. It should be re-assessed and a further injection given. This may entail the administration of even larger amounts by a different route, although later doses, even of larger amounts, cannot wholly compensate for the deficiency of the first.

Although no rigid scale of dosage for concentrated diphtheria antitoxin can be laid down, the following from the L.C.C. Departmental Report on Dosage of Antitoxin in Diphtheria is widely accepted :—

TABLE XIV

Clinical Severity	Dosage of Antitoxin (Single Dose)	Route
Mild	2,000 to 10,000 units	Intramuscular.
Moderate	15,000 ,, 30,000 ,,	Intramuscular or intravenous.
Severe	30,000 ,, 100,000 ,,	Intravenous.

The minimum therapeutic dose of 2,000 units should be given only in those cases where, as in hospital, constant supervision is possible ; otherwise, the minimum dose should be 8,000 units. If, after assessment of the case, it is decided to give more than 20,000 units, the intravenous route should be employed, if possible, for the whole dose, otherwise for part of it.

In assessing the severity of a case of diphtheria and therefore the amount of antitoxin necessary, it must be remembered that the *later* the case comes under treatment the more serious the prognosis. Cases seen after the third day should be regarded as *late*. The variable fatality of diphtheria must be remembered. In mild types of the disease several days may

be available for successful antitoxin therapy; in severe types twenty-four hours may be the maximum.

3. **Glucose (dextrose)** is indicated for the toxæmia. It maintains a supply of energy to vital organs and is believed to protect the heart muscle against the effect of toxin. Whenever antitoxin is being given intravenously, 50 c.c. of a 40 per cent. solution of glucose should, if possible, be added. At other times 2 to 4 drachms three-hourly by mouth is usually well tolerated and should be continued for some days. If nausea or vomiting due to the disease prevent oral administration, the intravenous route should be used.

4. **Symptomatic Treatment.**—For *cardiovascular failure* the patient should be kept without pillows and the foot of the bed slightly raised. No food should be given by mouth, but glucose administered rectally or intravenously. Radiant heat from a cradle which allows circulation of air may prevent coldness of the extremities. Drugs are of doubtful value: strychnine, atropine, coramine and adrenalin are used. Digitalis is contraindicated. Morphia in repeated small doses may tide a patient over a dangerous period of restlessness.

For *paralysis of the palate* thickening of fluids prevents regurgitation.

For *paralysis of the pharynx* the foot of the bed should be raised to promote drainage of mucus through the nose and prevent broncho-pneumonia. The pharynx can be kept clear of residual mucus by frequent mechanical aspirations or digital swabbing. Nasal or rectal feeding is essential, and glucose should be given, as patients lose weight rapidly.

For *paralysis of the diaphragm*, prolonged artificial respirations by a mechanical respirator, *e.g.*, Drinker's, may be necessary for seven to fourteen days. Many such cases also suffer from paralysis of the pharynx and the treatment for this must be combined with the artificial respirations.

5. Recently treatment of diphtheria by *combined active and passive immunity* has been introduced. 0·1 c.c. of formol toxoid (150 Lf. per c.c.) is given followed in twenty minutes to one hour by an appropriate dose of antitoxin, injected as far away as possible from the toxoid. Two days later a further dose of toxoid (0·3 to 0·5 c.c.) is given, followed at five-day intervals by 1 c.c. and 2 c.c. Good results are reported, particularly a diminution in the frequency of paralyses, by Ramon (1938) and others.

6. Concentrated antitoxin prepared by precipitation methods contains, say, 2,500 units per c.c. The recent method of enzyme disaggregation (protein digestion) followed by differ-

ential heating results in a smaller antitoxin-globulin molecule with increase in concentration, say 6,000 units per c.c., so that the volume and protein content of the therapeutic dose is much reduced. Better therapeutic results and a notable absence of serum reactions are claimed.

TREATMENT OF LARYNGEAL DIPHTHERIA

In addition to antitoxin, the treatment of laryngeal diphtheria is either expectant or operative. The former suffices in mild cases and may obviate the necessity for operation in a number of moderately severe cases. Operative measures are necessary where the seriousness of the attack, the progression of the dyspnœa and restlessness, or the severity of paroxysms indicate that relief is not being provided. If delayed until cyanosis appears, the prognosis is much worse. The following measures should be adopted in the order given :—

1. Administer *antitoxin* (see pp. 162, 163).
2. *Direct laryngoscopy* is desirable if possible—
   (*a*) To *inspect* the larynx for membrane.
   (*b*) To *swab* the larynx directly for *C. diphtheriæ* (swabs of nose and throat should also be taken).
   (*c*) To *aspirate* mucus and membrane, using a mechanical (electrical) suction apparatus ; it is thus sometimes possible to remove considerable quantities of membrane, relieve dyspnœa and avoid operative measures.
   (*d*) To perform *direct intubation* should this be necessary.

In experienced hands, direct laryngoscopy can be performed rapidly, without an anæsthetic, and with relatively little discomfort to the patient. Instruments for tracheotomy *must be at hand* in case aggravation of the obstruction demands immediate relief.

3. *Expectant Measures.*
   (*a*) *Antispasmodics : Steam* should be used to moisten the air around the head of the bed ; no tent is necessary. The patient should be kept flat. Atropine or belladonna is occasionally helpful.
   (*b*) *Counter-irritants* such as poultices and antiphlogistine to the neck sometimes provide relief.
   (*c*) *Sedatives, e.g.,* chloral and bromides, diminish restlessness which increases dyspnœa.

4. *Operative Measures.*

(*a*) *Aspiration* is mentioned above. If it provides relief it may be repeated two or three times a day until dyspnœa subsides.

(*b*) *Intubation* may be performed by sight through a direct laryngoscope, or by the old method of touch, in which the finger of the physician, passed over the base of the tongue, guides the tube into the larynx. The tube provides a rigid channel for air through the obstruction in the larynx. A flange at the upper end of the tube rests upon the opening of the glottis and prevents it from falling into the trachea. Those who practice routine intubation believe it to be superior to tracheotomy. In the hands of the experienced it is easy to perform and results in little shock. The air reaching the lungs is warmed and moistened by the natural processes, and the frequency of broncho-pneumonia is less than in tracheotomy. No scar is left and convalescence is more rapid. Intubation, however, has disadvantages: the tube is readily coughed up, and an experienced operator must always be close at hand to replace it; if there is much œdema of the larynx, there is danger of ulceration from pressure; and if membrane is present in the trachea below the tube, relief is not provided. Even when intubation is used as a routine, instances occur when tracheotomy is essential: it is the only operation in *extreme emergency*.

(*c*) *Tracheotomy* provides an artificial airway into the trachea, below the site of the obstruction in the larynx. The opening is maintained for three or four days by inserting a tube into the incision. If the finer points in the technique are not rigidly observed, the fatality from the operation is considerable.

The operation must not be deferred until the patient is cyanosed. In an extreme emergency speed is vital, but in all cases delays must be avoided. Everything and everybody must be ready before the operation. The patient should be prepared in bed, the arms being pinioned to the sides by a blanket wrapped and pinned around the trunk. Immediately

he is placed on the table the operation should begin. Deaths on the table rise in geometrical progression with the time the patient is kept waiting with an extended head and stretched neck. No anæsthetic is required. A pillow under the shoulders brings the trachea nearer the surface. Throughout the operation the head must be kept absolutely still and straight, as any deviation to the right or left moves the trachea from the midline. The operator must be sure of his landmarks before starting. The index finger of the left hand defines the cricoid cartilage and the thumb and middle finger hold the larynx and trachea on either side. The first incision cuts the skin, the second enters the trachea between the cricoid cartilage and the isthmus of the thyroid gland; or one "stab" incision may go straight through. The incision is made just below the cricoid cartilage and must be exactly in the midline or the trachea may be missed. (The calibre of the trachea in children under five years is about that of a cigarette.) No attempt must be made to proceed with the next stage unless the operator is satisfied that the trachea has been opened: this is readily known as air rushes in and out and the patient sometimes coughs. Some instrument must always be kept in the incision or the opening into the trachea may be lost. With the scalpel still *in situ*, a dilator is passed down beside it and the scalpel then removed. The dilator sets up coughing and membrane may be expelled. If relief of dyspnœa is not apparent at this stage, membrane may be present below the incision. Attempts should be made to remove it with membrane forceps, keeping the dilators in place. Bleeding rapidly stops when the tube is in position. It should be slipped in between the blades of the dilators, which are then removed. The operator, first ascertaining that the tube is in the trachea (by feeling the air enter and leave) and that bleeding has ceased, should tie the tapes of the tube securely round the neck and finally insert the inner tube. The operation should be performed in a few seconds to a few minutes. Oxygen should be at hand, and pituitrin (0·25 to 0·5 c.c.), injected *before* incision, diminishes shock.

The tube is changed in twenty-four hours and may be removed entirely in three or four days.

Broncho-pneumonia, surgical emphysema and "retained tube"—inability to dispense with the tube—are occasional complications.

Freedom from Infectivity.—The criteria of recovery from diphtheria are two—*clinical* and *bacteriological*. Of the former, ability to walk well, general fitness and the absence of

discharges and complications are the most important. The bacteriological standard consists in two negative cultures of the nose and throat, taken at intervals of not less than forty-eight hours, preferably a week. When the local lesion of diphtheria subsides, *C. diphtheriæ* disappear from the site with varying rapidity. In some cases, by the time the membrane has gone, the organism can no longer be detected; but generally the process of clearance is slower. In the first six weeks some 80 per cent. of patients are free. About 5 to 8 per cent. remain positive after the twelfth week and are then considered *convalescent carriers* (*vide infra*). The administration of antitoxin for therapeutic purposes, by providing passive immunity, converts the patient from the Schick-positive to the Schick-negative state. When this effect wears off (in two or three weeks) most patients remain Schick-negative from the active immunity induced by the disease. A few return to the Schick-positive state and are therefore liable to *second attacks*. The recent introduction of combined antitoxin and toxoid may prevent this occurrence. If the method is used, an additional immunological test (Schick test) should be employed to determine if active immunisation has been effective.

Diphtheria Carriers.—Two types of diphtheria carriers occur :—

1. *Convalescent Carriers*—who have recently recovered from an attack of the disease but continue to harbour the organism.
2. *Contact Carriers*—who have been exposed to a source of infection (a case of the disease or another carrier) but have not suffered from the disease. In an urban district where diphtheria is endemic a large percentage of the population is at some time infected with *C. diphtheriæ.* Among susceptible (Schick-positive) persons, this may result in a clinical attack, but more commonly in a latent infection, during which the organism persists for a few hours to a few days and then disappears. Such Schick "positive" carriers are rarely a source of danger to others. Infected immune (Schick-negative) persons usually throw off the organisms rapidly, but in some they persist for varying periods of days, months or even years. These are the true *contact carriers,* and as they may remain undetected for a long time they are important *reservoirs* of infection.

Carrying, whether by contacts or convalescents, may be *intermittent* or *continuous* (*persistent*). Intermittency, in many cases, is due to repeated re-infection. *The chronic, persistent carrier harbours the organism in greatest numbers and is a profuse disseminator of infection.* Carriers of *gravis* strains tend to be more chronic (Clauberg, 1935), and attention should be focused on them as they produce a severer type of the disease.

The most common sites for carrying are the nose, throat, ear, or combinations of these. Some underlying chronic non-diphtheritic abnormality at the infected site is commonly present and is an important factor in the maintenance of the carrier state. In the nose rhinitis is common : it may manifest itself as rhinorrhœa, or a fine crusting of the mucosa, or less commonly by atrophic rhinitis with large adherent crusts. An important variety in children is the low-grade rhinitis set up by the presence of a *foreign body*. Enlarged adenoids and unhealthy tonsils are common sites for carrying. The nasal sinuses are occasionally reservoirs. Aural carriers are common. When a patient with an abnormal nasopharynx and subacute or chronic otorrhœa becomes a carrier, the *C. diphtheriæ* may invade the middle ear and be detected in the discharge ; usually the organism is also to be found in the nasopharynx.

The **diagnosis** of the carrier state depends upon the detection of *virulent C. diphtheriæ* in a "healthy" Schick-negative person. Carriers of *gravis* and *intermedius* strains may, for practical purposes, be considered virulent carriers, but all *mitis* strains should be subjected to virulence tests. The carrier state **should never be diagnosed** from a simple morphological report upon a swab without further investigation of the organism and knowledge of host's state of immunity.

At any time about 1 to 5 per cent. of the child population are carriers, and just before an outbreak of the disease the percentage may rise to 15 or 20 per cent. A large number who carry the organism temporarily are no danger to others, and are developing their own active immunity. Unsystematic hunting out of carriers by indiscriminate swabbing is therefore to be deprecated. The object of investigating contacts should be to detect the *chronic persistent carrier*, and the best criterion as to the necessity for swabbing is the local *clinical* condition of the upper respiratory tract.

Success in treating carriers depends upon the ability to deal with the abnormal mucous membrane of the upper respiratory tract. Where infection is localised to tonsils or adenoids their removal readily clears up the carrier state.

When, however, the mucosa of the nose or nasopharynx is involved, treatment is less successful and relapses readily occur, particularly following a cold or re-exposure to the organism. Local application of "dimol" snuff, alkaline douches, argyrol and glycerin, iodine oil sprays, dyes (*e.g.*, methylene blue) and disinfectants (*e.g.*, formalin) are used. Autogenous vaccines have not produced better results than other methods. Fresh air and sunlight (U.V.L.) are valuable adjuncts. If a foreign body is present in the nose its removal, followed by local treatment, usually results in rapid cure.

PROPHYLAXIS

Active Immunisation.—*Diphtheria is a preventable disease*, but in order to eliminate it from the community a high percentage of children of pre-school and school age must be immune (at least 50 per cent. and 33 per cent. respectively). Active immunisation of susceptible children can protect 90 to 99 per cent. of them. The procedure outlined below is not always carried out in its entirety when mass immunisation is practised :—

1. Preliminary Schick test to determine susceptibility or immunity—sometimes omitted in young children in whom the proportion of susceptibles is high.
2. A course of two or three injections of the immunising agent to susceptible subjects, or to all if (1) is omitted.
3. A post-Schick test about six to eight weeks after the last injection to determine if immunity has been successfully established ; the long interval is necessary as immunity tends to develop slowly.
4. In a small percentage of cases the ordinary course is insufficient and further immunising injections (1 to 3) are necessary—followed by another Schick test.

The Schick Test is a simple and dependable skin test which indicates with considerable accuracy the capacity of the body to resist diphtheria. 0·2 c.c. of diluted diphtheria-toxin-filtrate (containing $\frac{1}{50}$ M.L.D. of toxin) is injected intradermally into the flexor aspect of the forearm. If an inflammatory reaction (a flush of 10 to 30 mm. diameter) is produced the test is positive and the subject is *susceptible* to diphtheria ; if no reaction results the test is negative and the individual *immune*. Formerly it was believed that a negative result could only occur if the amount of antitoxin in the blood available for

TABLE XV

SCHICK TEST

Result of Test	**Test Arm** (Left) Toxin+Protein Injected	**Control Arm** (Right) Protein Injected	**Cause of Inflammation**	**State of Immunity**
1. **Positive**	Reaction	No reaction	Toxin	Susceptible.
2. **Negative**	No reaction	No reaction	...	Immune.
3. **Pseudo (and negative)**	Reaction	Reaction (same size, intensity and duration as in test arm)	Protein	Immune.
4. **Pseudo+positive**	Reaction	Reaction (smaller, fainter and more evanescent than in test arm)	Protein and toxin in test arm. Protein in control arm	Susceptible.

neutralising the test dose of toxin was $\frac{1}{250}$ unit per c.c. or more. It is now known that such a result can occur with a much lower antitoxin level (Parish and Wright, 1938). The reading of the results of a Schick test is not quite so simple as described above because *false reactions* occur due to the presence of

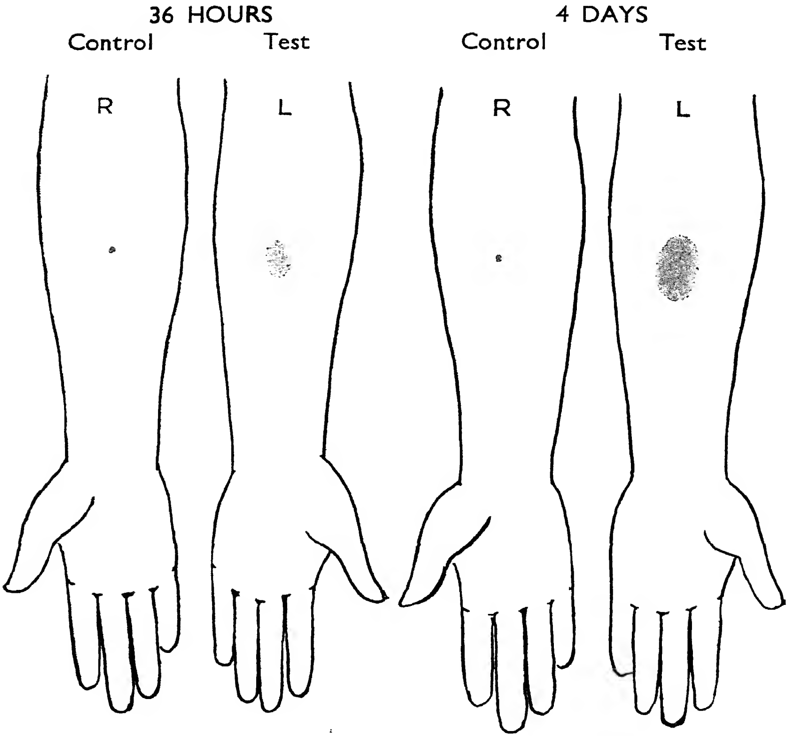


FIG. 17.—Schick Test. (*a*) Positive reaction.

bacterial proteins in the test solution. It is therefore necessary to control the test by the injection into the opposite forearm of a heated solution of the test fluid. Heating destroys toxin but leaves bacterial proteins. If a reaction occurs in the control forearm it is obviously a *false* one (*pseudo reaction*).

The *four* possible results of a Shick test are given in Table XV.

False reactions appear earlier and are more evanescent than true ones. A false reaction is at its maximum in thirty-six hours and has commonly disappeared in three or four days, whereas a true reaction reaches its maximum after the pseudo reaction has faded. False reactions are the result of specific

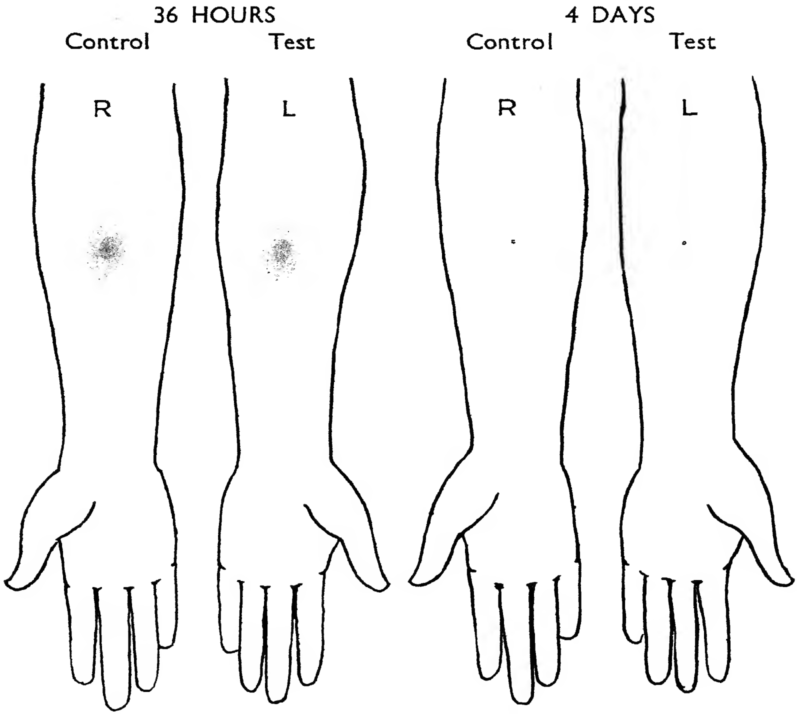


FIG. 18.—Schick Test. (*b*) Pseudo (and negative) reaction.
(A negative reaction without the pseudo element is not illustrated.)

hypersensitiveness to the bacterial proteins of diphtheria bacilli (see Chapter III). They indicate that the subject has been previously exposed to the organism and has therefore had an opportunity of acquiring immunity. For this reason pseudo+positive reactions are uncommon.

Schick tests are read in twenty-four to forty-eight hours and again in five to seven days. At the second reading doubtful

earlier reactions can be confirmed and *late positive reactions* which occasionally occur will be detected. A true positive test usually pigments and desquamates before fading. Fine linear striæ can be observed on the pigmented area.

Prophylactic Injections.—The chief qualities required of a

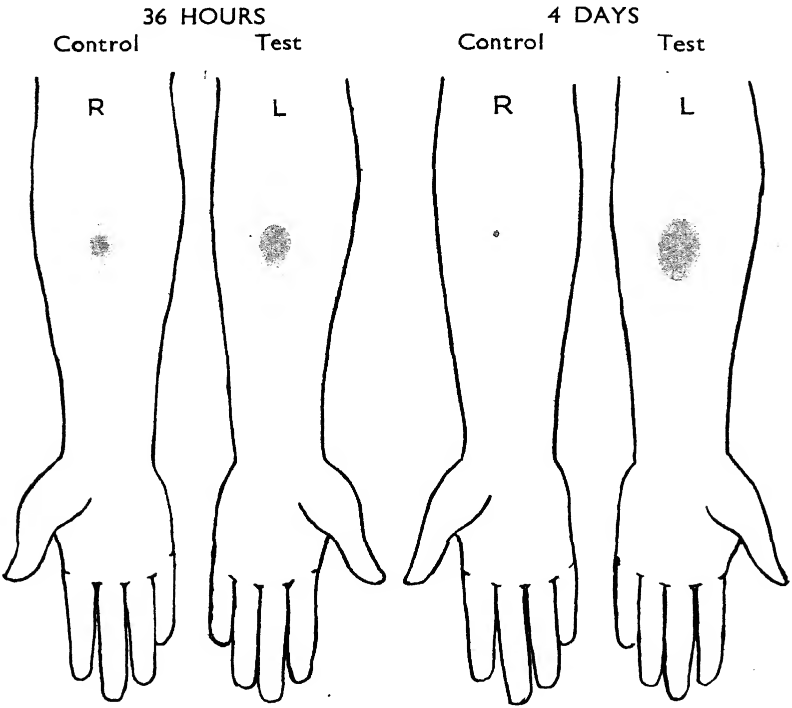


FIG. 19.—Schick Test. (*c*) Pseudo + positive reaction.

prophylactic are antigenic potency and a capacity to immunise by few injections with no unpleasant reactions. Several prophylactics are available and are listed in Table XVI. All are varieties of toxoid, *i.e.*, toxin which has been modified by formalin and heat so that the toxic power is destroyed but the antigenic power is retained. The potency of toxoid is sometimes described in "antigenic" or "immunising" units per c.c. (written Lf.—limit of flocculation—because of the laboratory

TABLE XVI

Prophylactic	Immunising Power	Liability to Cause Reactions	Dose	No. of Injections	Interval between Injections	Remarks
Formol-toxoid (F.T.)	Very high	Greater than with T.A.M. and T.A.F.	1 c.c.	3	Two to three weeks	Rapid in action. Chief drawback: liability to cause reactions in older patients.
Alum-precipitated toxoid A.P.T.	Very high	Greater than with T.A.M. and T.A.F. Local nodule is the rule—usually painless. Rarely a sterile abscess	(*a*) 0·2 c.c. (*b*) 0·5 ,,	2	Four weeks	Absorbed slowly, therefore a single dose produces slow, prolonged, immunising action.
Toxoid-antitoxin mixture (T.A.M.)	Moderate	Low	1 c.c.	3	One week	Obsolescent. Chief drawback: presence of antitoxin — liability to cause serum sensitivity.
Toxoid-antitoxin floccules (T.A.F.)	High	Very low	1 c.c.	3	Two to three weeks	Most useful for individuals who "react" to other types, *e.g.*, older patients.

(Jensen's Method: An initial subcutaneous injection of F.T. mixed with a sterile suspension of aluminium hydroxide, followed by *intranasal* instillation of 10 drops of F.T. at weekly intervals.)

method used in the standardisation of toxoid). Antigens used have an Lf. of 40 to 150, but dosage is usually prescribed in cubic centimetres and not in antigenic units, as the Lf. dose is *not* an exact measure of antigenic potency.

First injections do not stimulate antibody response so readily as subsequent ones, particularly in those who have no basal immunity, *i.e.*, have not had the opportunity of acquiring some immunity from contact with the organism. This is a recognised immunological phenomenon. First injections act virtually as "primary stimuli" (Glenny). Subsequent ones given after an interval—the longer the better—act as "secondary stimuli," provoke greater immunity response, and should be regarded as essential to secure a high level of protection. Hence "one-shot" methods, *e.g.*, a single injection of A.P.T., are not sound practice.

Reactions occasionally follow injections and are due to sensitiveness to bacterial proteins contained in the prophylactic. They rarely occur in children under five and their frequency increases with age. Reactions, which are more likely after some prophylactics than others, are rarely severe and never dangerous. A *local* reaction—swelling, redness and tenderness around the site of injection—is the most common and lasts for a few days.

General reactions occasionally occur within twenty-four hours and consist in pyrexia, malaise, headache, nausea and vomiting. Prophylactics containing serum (T.A.M.) occasionally produce serum disease, but the quantity of serum is very small and the reactions are usually slight.

The **Moloney test** was introduced to detect sensitiveness to immunising injections. It is performed by the intradermal injection of 0·2 c.c. of diluted toxoid. An area of erythema, with or without induration, occurring twenty-four to forty-eight hours later, is a *positive* reaction and indicates sensitiveness. The dose of prophylactic should be diminished or T.A.F. used. The test is unnecessary in children under eight years of age, most of whom are negative. A *pseudo* response to the Schick test provides comparable information, as it is due to the same sensitiveness to bacterial proteins (Mitman, 1936). Most pseudo and Moloney reactors have some immunity and require less prophylactic. The first small dose of A.P.T. (0·2 c.c.) may be used as a *detector* dose (Chesney). If a reaction follows, subsequent injections may be of T.A.F.

General Remarks.—The most suitable age to start immunising against diphtheria is in the second half of the first year of life ; failing this, all children should be protected before

starting school at five years of age. The duration of the immunity conferred is very variable. Once the Schick-negative state is attained, the individual commonly remains immune, particularly in urban districts where small latent infections

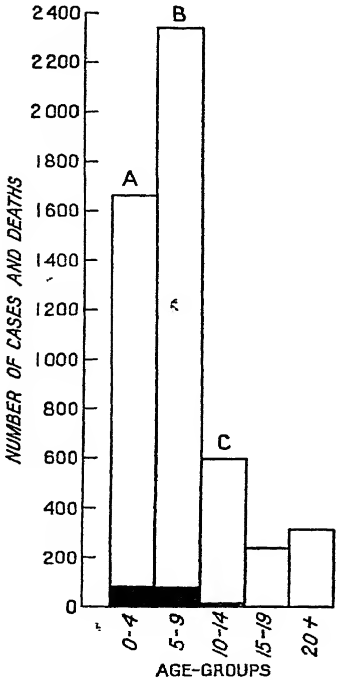


FIG. 20.—To show importance of immunising children of pre-school age. Immunisation on an adequate scale before school entry would reduce not only Column A but also Columns B and C, whereas immunisation only on or after school entry cannot affect Column A. Columns represent total cases of diphtheria and black portions the number of deaths.

(*By courtesy of the Editor of* THE LANCET.)

help to maintain immunity. Sometimes there is a relapse to the Schick-positive state two to five years later; rarely this may occur within a few months. It is therefore desirable to give an occasional "refresher" dose at intervals of, say, two years, or just before the child starts to go to school. It is usually more convenient to give the dose than to perform

another Schick test. It has been estimated that in Great Britain, of 100 children born and not immunised 10 will contract diphtheria and 1 will die; of every 100 children immunised, 1 will contract a mild form of diphtheria and none will die.

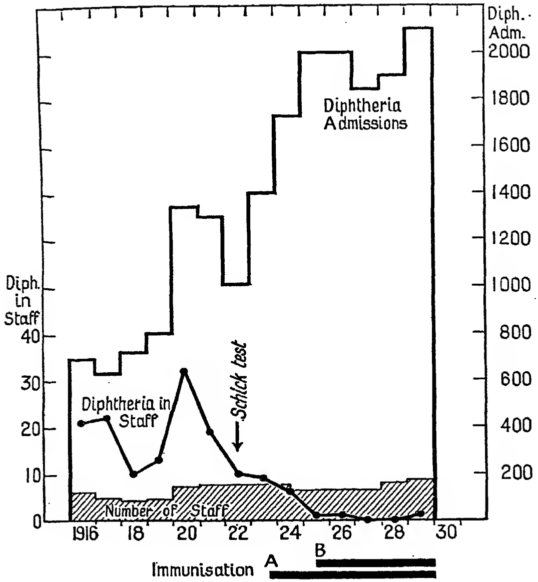


FIG. 21.—Showing effect of immunising staff of Birmingham City Hospital against Diphtheria. Columns=diphtheria admissions, and curve=staff cases of diphtheria. The first stage was the grouping of immune and non-immune nurses by Schick test (arrow). Only Schick-negative reactors allowed to work in diphtheria wards. Later the proportion of immunes was increased by active immunisation; later still the domestic staff was similarly treated.

(*By courtesy of the Editor of* THE LANCET.)

Passive Immunisation.—Temporary protection of exposed susceptible children may be conferred by the injection of 1,000 to 2,000 units of diphtheria antitoxin. This immunity cannot be depended upon for more than two weeks. The method is of value for familial contacts and in the control of ward outbreaks. It may be followed by active immunisation after an interval.

SUMMARY OF CHAPTER XIII

Strains of C. diphtheriæ: *Gravis* and *intermedius*—virulent; *mitis*—sometimes non-virulent.

Clinical Stages: (i) Membrane and toxæmia.
(ii) Cardiovascular impairment.
(iii) Paralyses.

Clinical Types: Anterior nasal, tonsillar (faucial), pharyngeal, laryngeal, non-respiratory.

Diagnosis of Doubtful Cases: Schick test and swabbing for virulent *C. diphtheriæ*.

Schick Test: (i) Negative and (ii) pseudo (negative)=immune. (iii) Positive and (iv) pseudo+positive=susceptible.

Treatment: Antitoxin—adequate amount in a single dose by an appropriate route; for laryngeal—conservative or operative measures to relieve obstruction.

Carriers: (*a*) Convalescent and (*b*) contact may be (i) transient, (ii) intermittent, (iii) chronic, persistent.

Active Immunisation by F.T., A.P.T., T.A.M., T.A.F.

Passive Immunisation by diphtheria antitoxin.

CHAPTER XIV

FUSO-SPIRILLOSIS

(*Plaut-Vincent's Disease, Vincent's Infection, Vincent's Angina*) *Ulcerative Stomatitis, Trench Mouth, Ulceromembranous Tonsillitis*)

DEFINITION.— An infection of the mouth, fauces and pharynx causing ulceromembranous lesions and gingivitis. Extension to the bronchial mucosa (bronchial spirochætosis) may occur.

Bacteriology.—Two organisms growing in symbosis are responsible for the disease, although the relative importance of each and their relationship with one another is still uncertain. They are a "spirillum" (spirochæte), *Treponema Vincenti*, and a fusiform bacillus, *Fusiformis fusiformis*. Both are delicate and grow only under anaerobic conditions. They may be found in normal mouths, but in the lesions of the disease they are usually present in large numbers. They can be detected by staining a direct smear of the lesion with weak carbol fuchsin, methylene blue or Leishman's stain.

Incidence.—The disease occurs at all ages, but is commoner in children and young adults and among the poor. It is only mildly infectious, but outbreaks appear in institutions, residential schools and among troops. Although the disease may affect healthy subjects, general ill-health predisposes to it and permits a quiescent infection to assume a clinical form. It is therefore likely to occur and to be most acute and severe in those debilitated by other infectious diseases such as measles, diphtheria, scarlet fever and typhoid fever; and it may complicate the buccopharyngeal lesions of scurvy, metallic poisonings, *e.g.*, mercury, lead, bismuth and phosphorus, and the blood diseases, *e.g.*, agranulocytosis and acute leukæmia.

Clinical Features.—The incubation period is unknown. The disease is conveyed by direct contact, *e.g.*, by kissing, and indirectly by infected utensils. Subjective symptoms are not striking: sore throat, dysphagia and an offensive breath are the commonest. General symptoms are usually trivial, except in the acute type complicating serious general diseases. The commonest sites affected are the gums, fauces, pharynx and

buccal mucosa. The disease may start in any one of these situations, but the gums, particularly adjacent to a carious molar, are the most frequent sites. The gums are swollen and red, and bleed easily ; the gingival margin is retracted and may be ulcerated. The infection, with or without ulceration, may spread along the gums, involving both upper and lower gums. The ulceration may extend deeply, loosening the teeth, which may fall out. It is important to realise that in the mildest cases the only feature is a non-ulcerative "gingivitis" with halitosis and no other symptoms.

In other situations the lesion consists of an ulcer, sometimes superficial, sometimes deep and spreading, covered with a friable, dirty yellowish-grey exudate which may largely obscure the ulcer. This membrane can be removed with difficulty, causing bleeding and exposing the ulcer. Multiple lesions are often present. The gums are affected in most cases, although the degree of involvement may be so slight as to be overlooked. *Cancrum oris* and *noma* (*vide* Chapter XVI, Measles) are also due to the same symbosis.

The regional lymph glands are usually enlarged and tender. Pyrexia and general disturbance are not marked except in those with an underlying general disease. A secondary anæmia frequently supervenes.

The condition may be acute, subacute or chronic. The frequent association of acute forms with general conditions is mentioned above. The chronic form most commonly affects the gums, and in such cases there is a tendency for relapses to occur with lowered states of the general health.

If properly treated the ulcers clear up readily, but the infection in the gums often proves resistant and tends to become chronic. The existence of a general disease may, however, interfere with the response to treatment. Deaths are usually due to associated diseases, although occasionally erosion of important structures by the ulcer may be responsible.

Differential Diagnosis.—1. GENERAL DISEASES.—In acute cases there are two immediate considerations :—

(*a*) To confirm the diagnosis by direct smear.

(*b*) To exclude general diseases such as *monocytic angina, agranulocytosis, acute leukæmia, poisoning by metallic substances, etc., even if the diagnosis of Vincent's disease is confirmed.*

2. DIPHTHERIA.—Ulceration is absent. The typical membrane appears to be deposited on the surface. The gums and cheeks are rarely affected and the type of fœtor is different.

The Schick test is positive and swabs show the presence of *C. diphtheriæ*. The condition responds readily to the specific antitoxin. The association of diphtheria with Vincent's angina sometimes occurs.

3. CHANCRE OF TONSIL.—The lesion is more swollen and indurated; the gums are not affected, fœtor is absent, and the *T. pallidum* can be detected on dark ground illumination. Lesions of secondary syphilis may be present and the Wassermann reaction is then positive.

Treatment.—Since the causative organisms are anaerobic, the principles of treatment are :—

(i) To clean the surface of the lesions so as to provide free access to air and to permit the application of local remedies.
(ii) To apply oxidising agents.
(iii) To exhibit treponemicides.

Cleaning the lesions presents most difficulty in the case of the gums. They should receive attention in the first instance from a dentist. Tartar should be removed and, if the patient's condition permits, carious and loose teeth should be extracted. The surface of the ulcers may be cleaned by gentle scraping, and the gingival pockets by syringing. Bowdler Henry (1936) recommends the use of a de Vilbiss dental spray containing normal saline and connected through a reducing valve to a cylinder of oxygen. The hygiene of the mouth after meals is important. The gums and the interdental spaces should be sprayed to remove food debris.

The oxidising agents may be used as mouth-washes or as local applications to the lesions. Sodium perborate is applied as a powder and hydrogen peroxide or a saturated solution of sodium chlorate are applied on a swab.

The treponemicides used are the arsenical preparations. Thrice daily application of dry neosalvarsan—applied with a throat swab dipped in glycerin—is the most successful. Intravenous administration of arsenicals is seldom necessary.

SUMMARY OF CHAPTER XIV

Features : Ulceromembranous lesions of gums, tonsils, pharynx and buccal mucosa ; gingivitis ; halitosis.

Organism : *T. vincenti* and *F. fusiformis* found on direct smear.

Treatment : Cleaning up—exposure to air or oxygen. Application of oxidising agents and treponemicides.

CHAPTER XV

WHOOPING-COUGH

(Pertussis)

DEFINITION.—Whooping-cough is a specific infectious disease of the respiratory tract caused by the bacillus of Bordet-Gengou (*Hæmophilus pertussis*). Typically, an initial catarrhal stage merges into one characterised by a paroxysmal cough. The paroxysms culminate in a long-drawn inspiration through the narrowed glottis giving rise to the high-pitched whoop from which the disease derives its name. Atypical attacks confined to the catarrhal stage and those in which the paroxysmal stage aborts, or is highly modified, are of common occurrence and probably outnumber typical attacks. From the preventive standpoint the recognition and management of the disease in its earliest stages is of the utmost importance, since it is then highly infective and most likely to be disseminated by droplet spray. During the paroxysmal stage, the whooping-cough of the public, the child is least dangerous to others, but in greatest danger himself from secondary infections of the respiratory tract.

Ætiology.—Whooping-cough is *endemic* in countries with temperate climate. Urban and especially industrial populations living in a crowded environment are those most affected. The disease exhibits periodical *epidemic* prevalence approximately every alternate year, sometimes concomitantly with measles. Localised outbreaks are much more usual than in measles although, ultimately, contiguous districts may become involved. Institutional outbreaks among young children are common.

Age Incidence.—Although attacks may occur at any age, the disease is pre-eminently one which affects infants under a year old and very young children. Attacks after the age of five years are relatively uncommon and after the age of ten years rare. *Second attacks*, especially abortive attacks, in the elderly whose immunity has waned are probably more frequent than is usually allowed. Since whooping-cough is not ordinarily a notifiable disease its real incidence is unknown. In London, however, Stocks and Karn (1932) estimated that 44 per cent.

of children are attacked before their fifth birthday, and 60 per cent. by the tenth year of age. Although lightly regarded by the public, whooping-cough is the most serious of the acute specific infections of children.

Mortality.—The annual number of deaths from the disease in England and Wales is from 2,000 to 3,000, but this does not represent the whole mortality since many deaths are ascribed to the main complication, broncho-pneumonia, to the exclusion of the primary specific infection. The fatality rate among children treated in hospital, a class selected on account of the severity of the attack or of poor home conditions, may be as high as 10 per cent. Whether in or out of hospital, nine-tenths of the deaths occur among children under five years of age ; the remainder among those aged from five to ten years ; over ten years of age fatality is negligible. Outstanding is the fatality rate of infants under three months of age : it may attain 90 per cent. In future, deaths from whooping-cough complicated by broncho-pneumonia are likely to be fewer owing to the use of the sulphonamide drugs in the treatment of this complication (*vide infra* Treatment).

Seasonal Prevalence.—Whooping-cough, like other acute respiratory infections, exhibits marked *seasonal prevalence.* The winter and spring months provide the largest number of cases and the most severe attacks, and also, as may be expected, the highest incidence of those complicated by broncho-pneumonia. It is the combination of infancy, the debilitating nature of the illness, which may last for many weeks, and the ever-present danger of superimposed secondary infections of the respiratory tract which makes an attack of whooping-cough such a perilous experience for the nursling.

Mechanism of an Epidemic.—P. Stocks (1933), as the result of a statistical study of the disease in London, concluded that during an epidemic, which is usually spread over a year, some children who escape a recognisable clinical attack acquire, as in measles, temporary latent immunity, the ratio of latent to recognisable infections being possibly between one and two. During the year succeeding the epidemic many children lose this latent immunity and are thus added to the number at risk. Then, he believes, " a sudden rise in the activity of the *H. pertussis* under seasonal influences at the moment when the herd-immunity becomes insufficient to withstand infection pressure upsets the balance of the interepidemic phase and the epidemic begins."

Bacteriology.—The causal organism is a small gram-negative hæmophilic bacillus isolated from the sputum of patients

suffering from the disease by Bordet and Gengou in 1906. The bacillus grows abundantly upon the ciliated epithelium of the trachea and bronchi in the early stages of the disease, but for its successful culture in the laboratory requires a medium containing defibrinated blood, preferably human blood. Upon such a medium the bacillus grows slowly, forming after some three days incubation small pearl-like colonies (*vide* Diagnosis). *H. pertussis* produces a neurotoxic endotoxin to which some of the manifestations of the disease are due. As the result of infection specific antibodies are produced in the blood (*vide* Diagnosis).

The view that *H. pertussis* is merely a concomitant, the real agent being a filterable virus, is maintained by a few workers, but the evidence which has been marshalled by Gardner (1936) is very strongly in favour of the generally accepted view that the bacillus is the sole causal organism. Gardner points out that—

(i) The bacillus is constantly present in the acute stages of the illness and is absent in other illnesses and in health.

(ii) The period of its expectoration coincides with the period of infectivity.

(iii) Specific antibodies are constantly demonstrable as the disease advances.

(iv) Intratracheal injection of pure cultures into apes results in an illness of entirely the same type as the human disease.

(v) Whooping-cough, as the Macdonalds (1933) showed, follows the intranasal instillation of pure cultures, and that whether from apes or human beings the organism is recoverable in pure culture from the lesions.

Two of the main points upon which those who uphold a virus causation rely are the occurrence of (i) interstitial pneumonia, and (ii) degenerative lesions of nerve ganglia, but, as Gardner says, interstitial pneumonia can be produced in animals by intratracheal injections of *H. pertussis* and other organisms, and the nervous lesions can be satisfactorily explained by the action of the powerful endotoxin produced by the bacillus and absorbed from the respiratory tract.

Pathology.—The pathological changes in whooping-cough result from the activities of the *H. pertussis* and its endo-neurotoxin and secondary bacterial infections, the respiratory tract and central nervous system being mainly affected.

1. *Respiratory Tract.*—The naked eye changes in the lungs in fatal cases of whooping-cough are most commonly those of broncho-pneumonia: lobar pneumonia is much less common. Some enlargement of the tracheo-bronchial glands is usual; in fatal cases associated with broncho-pneumonia the enlargement is considerable, and suppuration may be seen. Bronchiectasis is not uncommon. The histological appearances may be characteristic. Sections of the tracheal mucous membrane, suitably stained, may show abundant *H. pertussis* entangled in the cilia. A. R. Rich (1932) believes that the paroxysms are caused by the irritating action of these organisms, but the more general view is that the neuro-endotoxin formed by them sensitises nerve endings in the mucosa to expiratory stimuli.

Evidence of interstitial pneumonia is typical but not peculiar to whooping-cough; it occurs also in connection with influenzal pneumonia. Some degree of myocardial degeneration is usually present.

2. *Nervous System.*—Following death with cerebral symptoms there may be evidence of gross cerebral hæmorrhage, thrombosis or embolism. More common are multiple small meningeal hæmorrhages. On the other hand, there may be no naked-eye changes to account for death from convulsions and asphyxia, not unusual terminal events in infants. In such cases the specific neurotoxin has been held to be accountable.

The blood picture is discussed in the section on Diagnosis.

Incubation Period.—The incubation period to the commencement of the *catarrhal stage* varies from **seven** to **fourteen** days; the *paroxysmal stage* commences from **seven** to **fourteen** days later.

Clinical Features.—For the purpose of clinical description an attack of whooping-cough is conveniently divided into (1) the catarrhal stage and (2) the paroxysmal stage. It must be emphasised, however, that the disease is essentially an acute catarrh of the respiratory tract, and that the paroxysmal stage is to be regarded as a late and by no means constant epi-phenomenon.

1. *Catarrhal Stage.*—The catarrhal stage resembles an unusually persistent common cold. After a variable number of days of coryza accompanied by slight or moderate pyrexia the child develops a short harsh cough. The coughs, single at first, gradually become grouped and at length, usually first at night, definitely paroxysmal. Physical signs in the chest may be absent or confined to those of slight bronchitis.

It must be remembered, however, that broncho-pneumonia *may* develop in the catarrhal stage of the disease, caused either by *H. pertussis* or, more commonly, by secondary invaders. If broncho-pneumonia does occur and the child survives, the paroxysmal stage may be delayed or not be observed at all. In the uncomplicated case the temperature tends to fall to normal as the catarrhal stage merges into the paroxysmal stage.

2. *Paroxysmal Stage.*—Typically, the paroxysm commences

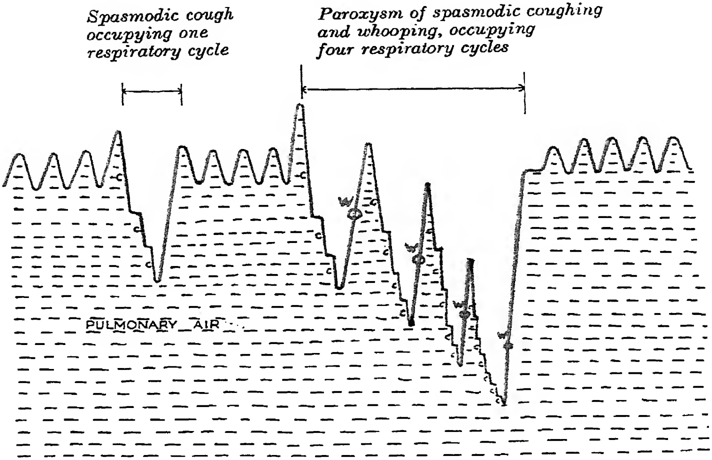


Fig. 22.—Diagrammatic Representation of the Respiratory Events in Whooping-cough.

Red = inspiration.
Blue = expiration.
C = cough.
W = whoop; the diminishing circles indicate an increasing pitch.

with a short toneless inspiration followed immediately by numerous short violent expirations in rapid succession. The child becomes much distressed, the cheeks are cyanosed, the lips purple and the conjunctivæ suffused. Saliva and stringy mucus dribble from the mouth. Except in babies who are unable to raise themselves, orthpnœa is the rule. After a series of these violent expirations during which the lungs are exhausted of air a long-drawn inspiration occurs. As the glottis is partially closed by spasm the inrush of air to the lungs produces a high-pitched sound known as the "whoop."

The paroxysm may comprise a single bout of coughs with a terminal whoop or there may be several such "phrases" without intermission, the whole paroxysm being punctuated by whoops and ceasing only when, following a whoop, the child ejects mucus and food debris frequently by the act of vomiting. Thereafter the child, although temporarily exhausted, rapidly resumes his normal appearance, except for a characteristic puffiness under the eyes, and in a few minutes either goes to sleep or returns to his toys.

Paroxysms are easily excited: feeding, emotion, or the sound of another child whooping may suffice to bring on an attack. Quite commonly there is no obvious exciting cause, although for a few minutes preceding the bout the child may appear uneasy and apprehensive and, if up and about, instinctively run to the nearest adult for help.

The paroxysmal stage is very variable both in severity and duration. Usually the number of paroxysms in the twenty-four hours gradually increases as the days pass up to a maximum which is maintained for several days. Always more frequent at night, the total number of attacks in the twenty-four hours may range from six or less to forty or more. After perhaps two weeks or more the paroxysms decline in frequency and severity; the terminal whoop is no longer heard. Next, the coughs return to the "grouped" type, then to single coughs and finally coughing ceases altogether. Some children, however, whoop, at least occasionally, for many weeks or months after the acute phase has passed, although they have long ceased to be either infective or ill: the whoop has become a habit.

Variations of the Paroxysm.—In infants and the aged the whoop may never be heard; the cough is spasmodic only. On the other hand, very young infants may suffer typical paroxysms. In infants, *paroxysmal sneezing* may replace the paroxysm of coughing wholly or in part. Occasionally in infants the whole paroxysm is represented by an attack of *apnœa* caused by spasm of the glottis and sometimes followed by convulsions.

Incidents of the Paroxysm.—During the paroxysm various small hæmorrhages may occur due to congestion of the vessels. *Epistaxis* is commonest; *subconjunctival hæmorrhage* less frequent; bleeding from the *membrana tympani* rare. True *hæmoptysis* and *hæmatemesis* are extremely rare. Gross *cerebral hæmorrhage* is an occasional occurrence and proves rapidly fatal. Minute cerebral and meningeal hæmorrhages may be discovered post-mortem.

Common *cumulative* results of the repeated paroxysms are :—

(i) Ulcer of the *frænulum linguæ*, the result of frequent projection over the lower central incisors ; an oval grey ulcer is produced.
(ii) *Herniæ*, particularly umbilical.
(iii) *Prolapse of the rectum*.
(iv) *Emphysema* of any type, including the interstitial form giving rise to "surgical" emphysema. Pneumothorax has occurred.

Complications.—1. *Respiratory*.—During the early catarrhal stage *acute laryngitis* is occasionally severe. A certain degree of *bronchitis* may be regarded as a normal feature of the disease, especially in the catarrhal stage. The outstanding and most fatal respiratory complication is *broncho-pneumonia*, which may occur at any stage. In the catarrhal stage it is most likely to be due chiefly to the *H. pertussis* ; in later stages to secondary invaders, *H. influenzæ*, *S. hæmolyticus* or the *pneumococcus*.

When broncho-pneumonia occurs in the catarrhal stage, the nature of the underlying specific infection may not be suspected, whilst the effect of this complication in the paroxysmal stage is to inhibit or modify the paroxysms for the time being ; the terminal whoop ceases to occur, but returns again if the child recovers from broncho-pneumonia. Lobar pneumonia is less common and perhaps less fatal. Either type of pneumonia may be followed by empyema.

2. *Gastro-intestinal*.—Acute enteritis or gastro-enteritis may occur at any stage of the disease in one of the three types, viz. :—

(i) *Dietetic*, due in infants to a change from breast to artificial feeding, and in older children to the difficulties attendant upon nutrition.
(ii) *Auto-infection* brought about by the swallowing of mucopus derived from the respiratory tract.
(iii) *Extraneous Infections*, which may be an infectious enteritis or bacillary dysentery, not uncommonly of Sonne strain, due to the contamination of milk sometimes infected by the fingers of attendants who have handled the stools, without proper precautions, of an unsuspected carrier in the ward. (See Chapters XXVIII and XXIX.)

3. *Nervous System*.—Convulsions rank next to broncho-pneumonia as a cause of fatality. They may succeed a paroxysm

or bear no apparent relationship to it, and may be due in some instances to cerebral congestion and in others to the action of the neurotoxin. Convulsions are more likely to occur in the rickety infant who is a potential subject of tetany. Occasionally fits of Jacksonian type are seen. Spasm of the glottis in infants has already been mentioned. Of rare occurrence are *bulbar paralysis*, *hemiplegia* and other palsies.

4. *Cardiac.*—A severe attack of whooping-cough may result in cardiac dilatation.

5. *Renal.*—Transient albuminuria is not uncommon. The occurrence of acute nephritis, which is very rare, should lead to suspicion of a secondary hæmolytic streptococcal infection.

6. *Special Senses.*—As in other acute infections of the respiratory tract in children, *otitis media* may occur as the result of infection caused by mucopus in the nasopharynx. The incidence of this complication varies with the age-grouping of the patients and with the conditions under which they are nursed.

Subconjunctival Hæmorrhage has been mentioned; the condition appears alarming, but is quite devoid of danger; the extravasated blood is absorbed in a few days. Rare ocular complications are *retinal hæmorrhages*, *detachment of the retina*, and *optic neuritis*.

Associated Infections.—As might be expected in very young children, almost any combination of the acute specific infections may occur. Concurrent measles is commonest, scarlet fever and diphtheria less common, but the occurrence of any particular second specific infection is fortuitous. Measles, by increasing the likelihood of broncho-pneumonia, adds to the gravity of the prognosis. The supervention of diphtheria is serious owing to the effect of diphtheria toxin upon heart muscle which may already be damaged by the attack of whooping-cough. Extraneous gastro-intestinal infections are mentioned above; the combination of whooping-cough and infectious enteritis in infants is particularly lethal.

Sequelæ.—Some degree of vesicular *emphysema* is to be expected after a severe attack. Broncho-pneumonia may result in *fibroid lung* and *bronchiectasis*. Radiological evidence leaves no doubt that some degree of fibrosis, with or without bronchiectasis is a common sequel of whooping-cough complicated by broncho-pneumonia. It is desirable that in every such case radiographs of the chest should be obtained, and that the child should be kept under periodical clinical and radiological observation until it is clear that the process has become quiescent. Like measles, an attack of whooping-cough may

light up a latent focus of *tuberculosis*, and in infants especially rapid dissemination may occur, but such a sequel is far less common than fibrosis.

Diagnosis.—The importance of the early diagnosis of whooping-cough from the preventive standpoint has already been stressed, but, unfortunately, diagnosis on clinical grounds in the early stage may be impossible unless the child, following a known exposure, is already suspect. Most cases of whooping-cough are diagnosed only when the paroxysmal stage has commenced, and this is largely due to the fact that even then, unless the patient is gravely ill as the result of superadded broncho-pneumonia, medical advice is not sought.

If contact is known to have occurred, as in an institutional outbreak, then the cause of a persistent catarrhal state with increasing cough can hardly be in doubt. The catarrhal stage may be confused with a common cold or allied influenzal conditions ; the duration of catarrh and the gradual development of a cough as the catarrhal symptoms wane are highly suspicious. A typical paroxysm of whooping-cough is unmistakable, but atypical or abortive paroxysms which are of frequent occurrence in infants and very young children and in the aged give rise to difficulty. Enlarged tonsils and adenoids are associated with catarrh and a harsh cough. Enlarged tracheo-bronchial glands give rise to a similar harsh cough. Bronchial asthma in children is sometimes confused, but the history of the attack or previous attacks, the wheezing character of the respirations and the high eosinophilia are conclusive.

There are now several accessory diagnostic procedures which, applied at the proper stage, may afford considerable assistance.

1. COUGH PLATES.—The most conclusive evidence that the patient is suffering from whooping-cough is the recovery of the causal organism from the droplet spray (Gardner and Leslie (1932)). Glass or aluminium petri dishes containing a freshly prepared medium of defibrinated, preferably human, blood (Bordet's or Sauer's modification of Bordet's medium) are exposed at a distance of from 4 to 6 in. from the child's mouth when it is in the act of coughing. The aim is to collect *spray*, not *sputum*, and it is wiser to expose two plates in succession in case one fails to collect the causal organism. After exposure the lids are replaced and the plates incubated. If positive, pearl-like colonies of the *H. pertussis*, which is of slow growth, are identifiable in the field culture on the third day. Care must be taken not to confuse colonies of the closely allied *H. influenzæ*, which grows more rapidly and is frequently

present in the respiratory flora of whooping-cough patients. Cough plates are positive in 75 to 80 per cent. of cases in the catarrhal stage; in 60 to 70 per cent. during the early paroxysmal stage; but are almost invariably negative if exposed when the child has been whooping for a month. This is in agreement with the clinical observation that a child who has been whooping for four weeks has ceased to be infective. Thus the cough-plate method is most valuable in the early stages of the disease. Positive plates are of course conclusive, but, owing to the practical difficulties of collection, no great reliance can be placed upon negative plates obtained from small children.

2. BLOOD COUNTS.—At the extremes of the attack, viz., the early catarrhal stage and the late paroxysmal stage, a blood count shows *leucopenia*. This is not peculiar to whooping-cough since leucopenia occurs at the onset of other infections as diverse as measles and enteric fever. When the paroxysmal stage commences, the blood picture changes to *leucocytosis* with a relative *lymphocytosis*. Gold and Bell (1936) consider that a suspicious spasmodic or paroxysmal cough associated with a leucocytosis of 12,000 or more, of which 60 to 80 per cent. are lymphocytes, is strong presumptive evidence of whooping-cough.

Thus, the white-cell count only becomes significant during the early paroxysmal stage, but lymphocytosis once established persists until the paroxysmal stage wanes.

3. SEDIMENTATION RATE (E.S.R.).—Gold and Bell (1936) found that during the *paroxysmal* stage the sedimentation rate of the blood was normal or retarded in 94 per cent. of their series. In other acute infections the rate is *accelerated*; an accelerated rate in obvious whooping-cough should lead to a suspicion of complications of bacterial origin.

Diagnostic Triad.—The same workers consider that the diagnostic triad of (i) suspicious cough, (ii) lymphocytosis with leucocytosis, and (iii) retarded (normal or subnormal) sedimentation rate is peculiar to whooping-cough.

4. COMPLEMENT FIXATION.—Specific complement fixation can be shown in a high proportion of cases of whooping-cough after about the third week from onset. A negative complement fixation does not necessarily exclude whooping-cough, but a negative followed later in the attack by a positive result is very strong confirmatory evidence. The same remarks apply to specific *agglutinins* which can similarly be demonstrated. Complement fixation cannot be demonstrated for more than a few months *after* the attack.

5. *Intradermal Tests.*—Intradermal tests for susceptibility have been carried out with whooping-cough vaccines. Readings, themselves equivocal, have been interpreted in diametrically opposed ways according to whether an "antitoxic" immunity or an allergic sensitivity was to be demonstrated. Tentative work has also been done with purified endotoxin; A. R. Thompson (1938) obtained an intradermal response to pertussis endotoxin, presumably allergic in character, in 85 per cent. of children with a past history of whooping-cough. Similar reactions occurred in 30 per cent. of individuals without history, and Thompson thinks this may be due to latent immunisation or recent contact with the causal organism. Bacterial hypersensitiveness is demonstrated by the tenth day of the disease and increases later; it ultimately regresses, but not completely. Thompson considers the intradermal endotoxin test may be of some value in diagnosis in early, atypical or late cases where the cough-plate method has proved disappointing.

Prophylaxis.—1. *Segregation.*—In order to be effective segregation must be early; much less is gained by the segregation of the child who is already whooping; the most infective phase has passed and the damage is done. A child who has been whooping for a month may be regarded as no longer infectious. The Medical Officers of Schools Association advises that children may return to school when the characteristic spasmodic cough has ceased for at least two weeks; or, in cases of persistent whooping, in not less than four weeks from the onset of the spasmodic cough.

R. E. Smith (1936) considers that these periods are arbitrary and should not apply individually. He bases this opinion upon the results of "release" cough plates; by obtaining negative cough plates he was able, on the average, to save twelve to fourteen days on the usual isolation period. He points out, however, that his results were obtained during fine weather and might not hold good during the winter months. It must also be observed that his patients were boys of public school age who could co-operate in the exposure of the plates. Nevertheless, the results of a number of observers show that the causal organism is recovered only very exceptionally from patients who have passed the fifth week of the disease.

2. *Quarantine.*—Exposed susceptible contacts should be kept under daily observation for three weeks, isolated at the first appearance of catarrhal symptoms and cough plates exposed.

3. *Disinfection.*—Concurrent disinfection or destruction of any articles soiled by the patient is important. By way of terminal disinfection, ordinary cleaning of the room suffices.

4. *Vaccine Prophylaxis.*—Until recently the results of vaccine prophylaxis were equivocal.

As the result of the work of A. D. Gardner (1936) in this country and L. W. Sauer (1935) in America, it is now clear that in order that vaccines may be successful in securing complete or at least considerable immunity to attack following exposure—

(i) They must be freshly prepared (Madsen) from organisms selected in the correct antigenic phase, *i.e.*, Phase I (Gardner), and grown upon a medium preferably containing human blood (Sauer). Stock vaccines not conforming to these conditions are useless.

(ii) The dosage must be adequate and, according to Sauer, at least four months should elapse between inoculation and exposure in order that a satisfactory degree of immunity may develop.

Both Madsen and Sauer use vaccines in strength of 10 million organisms per c.c., and both inject three doses at weekly intervals, but whereas the former attains a total dosage of 22 billion organisms by injections of 0·5, 0·7 and 1 c.c., the latter injects 2, 3 and 3 c.c.—an aggregate of 80 billion organisms : for children *over* two years old, doses of 2, 4 and 4 c.c. are recommended. Owing to the early age at which whooping-cough attacks, the sooner vaccine prophylaxis is carried out the better. Sauer suggests that the best time is between the seventh and tenth month of age. The immunity produced by vaccines is not of a high level, nor is it lasting.

Kendrick and Elderling (1939) observed for a period of forty-four months 1,185 vaccinated children and 2,397 controls. Among the vaccinated the number of attacks per 100 children per year of observation was 2·3 ; among the controls 15·1. Taking known exposure to infection into account, there were 12·5 attacks per 100 exposures in the vaccinated and 68·5 in the controls.

5. *Convalescent Serum.*—The serum of convalescents has been used by a number of workers for prophylaxis with, apparently, a measure of success. D. Paterson (1935) suggests a dose of 10 c.c., and R. E. Smith (1936) believes that in a considerable proportion of cases convalescent serum prevents or favourably alters the course of the disease if injected " before possible infection or in the incubation phase." If parental whole blood is used the dosage must be doubled. The results must be accepted with reserve : it is difficult to be sure that " effective " exposure has occurred and that attack would have followed if no serum had been injected.

Treatment.—1. *General.*—The patient must be provided with an abundance of fresh air. To nurse a child with an uncomplicated attack in a confined and airless atmosphere is to invite superimposed respiratory infections. (See Chapter XX, Measles, para. Treatment.)

Particularly because of the long and debilitating character of the illness adequate nourishment is important, but may be difficult to maintain. Any attempt to feed the child may result in a paroxysm and vomiting. Milk with added cream must form an important item of the dietary. Solid food should be finely divided and given slowly in small feeds in order not to excite coughing. With these precautions the dietary suitable to the child's age is indicated in the uncomplicated case.

2. *Therapy.*—(*a*) *Drugs.*—In spite of the large number of remedies which have been tried, the treatment of whooping-cough by drugs remains unsatisfactory. Treatment is palliative only ; the severity and frequency of the paroxysms may be diminished, but no one drug can be relied upon to effect this in all cases. Three only will here be mentioned as having proved of value in our whooping-cough wards.

(1) *Belladonna.*—This is probably the most valuable of the older remedies, but it must be given in progressively increasing doses before a therapeutic effect is obtained. The initial dose of $2\frac{1}{2}$ to 5 minims of the tincture contained in an expectorant mixture, three or four hours daily, must be increased each day until 10 to 15 minims of the tincture in each dose is being taken, depending upon the age of the child. The drug is tolerated well by children, but if marked signs of intolerance appear the treatment must be changed.

(2) *Ephedrine.*—Ephedrine by its action on the constrictors relaxes bronchial spasm, and for the moderately severe case is frequently successful where belladonna has failed : or it may be combined with belladonna. For an infant, the dose is $\frac{1}{12}$ gr. ; for a child of five, $\frac{1}{2}$ gr. Ephedrine is conveniently given in a simple linctus thrice daily. When improvement has resulted, morning and evening doses suffice.

(3) *Luminal.*—If the paroxysms are very severe and exhausting, it is advisable to try luminal, its effect being carefully observed and the drug withdrawn as soon as possible. For infants the *total daily dose* should not exceed $\frac{1}{8}$ gr. ; for children under five, $\frac{1}{2}$ gr. ; and for those over five, 1 gr. ; the *individual* doses being $\frac{1}{24}$, $\frac{1}{6}$ and $\frac{1}{3}$ gr. respectively.

Luminal (or soda-luminal) given in mixtures must be freshly prepared in small quantities. The tablets suitably

divided and dispensed as powders with lactose may be conveniently given in milk. Tablets must never be used for hypodermic injections: specially prepared ampoules are obtainable.

Recently the oral administration of vitamin C in the form of ascorbic acid has been advocated as having a very favourable effect upon the course of the disease. This is not proven. Leonard Parsons (1938), while agreeing that the artificially fed child must be given generous supplies of vitamin C, finds that there is no justification for its administration in large amounts as a therapeutic or even as a prophylactic measure in every variety of infection. Vitamin C is contained in orange juice, and given in this form probably suffices.

(*b*) VACCINE THERAPY.—There is no evidence, when the observations are properly controlled, that either vaccines (N. D. Begg and M. F. Coveney, 1936) or endotoxin (A. R. Thompson, 1937) is of any use in the treatment of the paroxysmal stage. Thompson thinks that endotoxin injected in the pre-paroxysmal stage may have some value. With either preparation troublesome reactions may occur in young children.

(*c*) *Convalescent Serum and Parental Whole Blood.*—The claims made for convalescent serum or parental whole blood in treatment, although better substantiated than those made for vaccines, are not convincing; nevertheless, either, injected very early, may be worthy of trial. Not less than 20 c.c. of pooled serum or double this volume of parental blood should be injected.

(*d*) *Physical Therapy.*—The results of either X-ray or ultra-violet ray therapy may be strikingly good in individual cases, but, like other methods, cannot always be relied upon. As a tonic for children debilitated by the attack, general irradiation by ultra-violet rays derived from carbon arcs is of undoubted value, especially, of course, during the winter months when natural sunlight is lacking.

The foregoing methods apply to the treatment of the *paroxysms*. The treatment of the important complications of *broncho-pneumonia* and *convulsions* from either of which, rather than from whooping-cough itself, young children die, demands consideration. The general management of *broncho-pneumonia* has already been mentioned (*vide supra* and Chapter VI), but as in the broncho-pneumonia of measles Thompson and Greenfield (1938) have found the sulphonamide group of drugs valuable, and this we can confirm from our own recent experience. The details of dosage are the same as those set out under the treatment of measles (Chapter XVI, p. 216).

Convulsions may not yield to the old methods of the mustard bath and the whiff of anæsthetic, and although these

may be tried, the most successful means of terminating an attack is to perform lumbar puncture. It is necessary to withdraw only a few cubic centimetres of cerebrospinal fluid.

SUMMARY OF CHAPTER XV

Causal Agent : *Hæmophilus pertussis.*
Clinical Stages : (i) Infectious, febrile, *catarrhal*—symptoms of a common cold.
(ii) *Paroxysmal* — afebrile paroxysms of coughing, whooping and vomiting.
Aids to Diagnosis : Cough plate, blood count, E.S.R., and complement fixation test.
Chief Complications : Broncho-pneumonia, convulsions, enteritis.
Sequelæ : Emphysema, fibroid lung, tuberculosis.
Prophylaxis : Vaccines.
Treatment : Symptomatic — sedatives and antispasmodics ; sulphonamides for broncho-pneumonia.

CHAPTER XVI

MEASLES (*Morbilli*)

DEFINITION.—Measles is characterised by a prodromal catarrhal stage, during which Koplik's spots appear in the mouth, followed by a generalised macular rash. In young children it is a serious disease because of the liability to broncho-pneumonia. Measles is intensely infective in its early stages.

Ætiology.—Measles occurs all over the world and is *endemic* among urban populations. At *two-yearly* intervals *epidemics* occur. They commence in the autumn, but in recent years, in London, have tended to lag in their advance until the end of the year. Thereafter advance becomes increasingly rapid, the peak being attained during March. From the end of that month the numbers of cases decline rapidly, and by August at latest the interepidemic phase recurs.

Owing to the fact that the peak of the epidemic is approached or attained at a season of the year when non-specific infections of the respiratory tract are ordinarily prevalent, the incidence of broncho-pneumonia rises not only absolutely but relatively to the number of attacks of measles.

This rise in the incidence of broncho-pneumonia and therefore in the fatality rate of measles occurs almost entirely among children under five years of age, and most markedly among those up to the age of two years.

The reports of the Medical Officer of Health of the London County Council upon successive epidemics of measles in London have shed much light upon the age-incidence and deaths from measles.

During an epidemic in London, which comprises all types of community, incidence falls most heavily upon toddlers and children of earlier school ages. *Fatalities* occur chiefly among those up to the age of three and particularly up to the age of two years. This is due almost entirely to the frequency and lethality of broncho-pneumonia among these groups (*vide* Complications). Halliday (1928) showed that in the tenements of Glasgow the maximum *incidence* of measles fell upon children under school age, but among the children of working and

middle-class families with improved accommodation the maximum incidence was upon children of school age, as in the case of London. Owing to the sheltered nature of their upbringing, children of the public school class contract measles still later. The poorer the environment, generally speaking, the greater is the number of victims of measles and its concomitant broncho-pneumonia.

The result of a frank unmodified attack of measles is, with few exceptions, solid active immunity, and thereafter a *second attack* is very rare indeed. If it occurs it is likely to be mild. The occurrence of measles among infants up to the age of three months is also very rare; the infant is protected by placentally transmitted passive immunity (see Infantile Resistance, Chapter II). After the first three months this passive immunity commences to wane, and by the eighth or ninth month, judging by the occurrence of unmodified measles among infants of this group, has entirely disappeared. Among infants over three months and under eight months of age, clinically recognisable measles occurs, but the attack is usually modified. This natural infantile resistance, securing naturally modified measles, occurs only in infants whose mothers have had measles, probably in childhood, themselves, and who are therefore actively immune. Non-immune mothers cannot transmit immunity, and the child may either be infected *in utero* by the mother, herself the subject of an attack, or may be infected after birth during the first three months of life.

During an epidemic most susceptible children who have been effectively exposed contract clinically recognisable measles. It is to be noted that although in the early stage measles is readily transmitted by droplet spray from one child to another, yet there are degrees of exposure. It has been estimated that in institutional outbreaks of measles "exposure" does not result in attack in a quarter of those exposed. Effective exposure is most likely to occur under the intimate conditions of home life. But, as Halliday (1928) and Stocks and Karn (1928) have shown, exposure of susceptible children in their homes, and therefore ordinarily "effective," does not always result in a clinically recognisable attack of measles. A proportion of children in every epidemic of measles, as the result of exposure, develops not a clinical attack and permanent active immunity, but "temporary" (Halliday) or "latent" (Stocks) immunity. This type of immunity protects the child for the time being, and these temporary immunes added to the number of recent active immunes tend to bring the epidemic to an earlier end than would otherwise be the case. But by the time the

next epidemic is due the latent immunity has disappeared and they are again at risk (although, be it noted, as they are several months older the risk of a fatal attack is not so great).

Bacteriology.—Although it has not so far been identified, there is general agreement that measles is caused by a filterable virus. The causal agent is present in the nasal secretions and in the blood only during the early stages of the disease. The virus of measles appears to render the mucosa of the respiratory and gastro-intestinal tract peculiarly susceptible to further damage by concomitant bacteria. Of these the overwhelming importance of the *hæmolytic streptococcus* has been repeatedly demonstrated. With relatively few exceptions the complications of measles of bacterial origin are due to strains of this organism: the *pneumococcus* and *H. influenzæ* are less frequently responsible.

Pathology.—During the prodromal stage of measles Warthin (1931), Hathaway (1935) and others have identified in the tonsillar and appendicular mucosa *giant cells* which they believe to be peculiar to the disease. These giant cells were not demonstrable in a series of autopsies of fatal cases of measles analysed by Degin (1937). In the same series no lesion definitely pathognomonic of measles was found; the most constant microscopic finding was an interstitial mononuclear cell infiltration possibly due to the hæmolytic streptococcus.

As might be expected in fatal cases of measles, the chief pathological changes are to be found in the lungs. In Degin's series of 100 autopsies, gross signs of pneumonia were present in 93 cases. Histological examination showed that in 50 per cent. the pneumonia was of interstitial type; in 17 per cent. lobular, while in the remainder there was a fairly equal distribution of both types. The laryngeal mucosa may be congested and œdematous or present evidence of ulceration. Generally speaking, the changes present in other organs, the heart, liver, spleen and brain, are those associated with acute toxæmic conditions, although cerebral damage suggestive of, or definitely due to, *encephalitis*, or evidence of otogenic *meningitis* may be found.

Blood Picture.—Piney (1931) states that leucocytosis occurs even during the incubation period. Leucopenia replaces leucocytosis when the temperature rises and during the appearance of the exanthem: it persists for about two days. Thereafter, in the uncomplicated case, the leucocyte count becomes normal or but slightly increased. The occurrence of complications of bacterial origin at any stage is reflected in leucocytosis. Relative lymphocytosis during which the

monocytes may attain 10 per cent. is usual in the febrile period according to the same authority.

Incubation Period.—The incubation period of measles to the commencement of the catarrhal stage is **ten** to **eleven** days. The catarrhal stage precedes the appearance of the rash by from three to four, and sometimes five days. The average incubation period to the appearance of the rash is **fourteen** days. Exceptionally long periods have been recorded, and in artificially attenuated measles (*q.v.*) the incubation period to the occurrence of the miniature attack is frequently prolonged to seventeen or eighteen days.

Loss of Weight.—(Meunier's Sign).—From the fourth to fifth day after infection, repeated weighings may reveal a progressive loss which continues to occur up to the early stage of onset. Advantage is taken of Meunier's sign in some boarding schools in order to pick out and segregate children incubating measles at the earliest possible moment.

Illness of Infection.—E. W. Goodall (1925) and others have described a febrile catarrhal attack sometimes accompanied by a fleeting rash occurring within a few hours of exposure to measles: to this the term "illness of infection" has been applied. The manifestations quickly disappear and are followed in due course by an ordinary attack of measles. The phenomenon is possibly of an allergic character.

Clinical Features.—I. *Stage of the Enanthem* (pre-exanthem or catarrhal stage).—Measles commences very much in the manner of a common cold. There is an abrupt rise of temperature to 102° to 103° F. or more, with corresponding increase in the pulse rate. The demeanour of the child changes: he is cross and miserable and disinclined for play or food. Coryza with an occasional sneeze and slight injection of the conjunctivæ are usually manifest on the first day. Next morning it is common for the temperature to have dropped a degree or more, but it rises towards evening, continues to rise perhaps to 104° F. and remains raised throughout the appearance and evolution of the rash, only falling as this fades. During the stage of the enanthem the catarrhal manifestations increase and reach a maximum just before the appearance of the rash. The coryza becomes more marked: a short harsh cough is characteristic, and there may be considerable laryngitis. Definite conjunctivitis, associated with a varying degree of photophobia, is usual.

Some observers have claimed that tenderness over the appendix region or a definite attack of *appendicular colic* is

not infrequent during the prodromal stage of measles, and would correlate this occurrence with the demonstration of giant cells in the mucosa of the appendix (*vide supra* Pathology). Laparotomy in such cases has revealed an appendix normal to the naked eye. On the other hand acute perforative appendicitis has occurred as a fortuitous complication. A differential blood count should precede surgical interference.

Examination of the buccal mucosa on the first day of the illness shows as a rule general injection. On the second day in a large proportion of cases *Koplik's spots* can be identified, and since they are pathognomonic of measles their identification as early as possible in what is the most infective stage of the disease is clearly of the utmost importance. In order to see Koplik's spots the cheek must be everted with a spatula and in daylight, sunlight if possible, but never if it can be avoided, artificial light, and search made in the neighbourhood of the papilla of Stensen's duct, which is just opposite the second premolar of a child. Koplik's spots are *minute,* pin-point, bluish-white specks, frequently compared with grains of salt, set upon a red base. They occur on both sides, although they may be far more numerous, or better developed, and therefore more readily seen on one side than the other. In number they may be comparatively few and discrete or so numerous as to become confluent upon the site of election, in which case the mucous membrane has the dull appearance of ground-glass (the "matt" surface of photographers). Koplik's spots, as E. W. Goodall (1928) has recorded, may be found at autopsy upon the tracheal mucous membrane. Other occasional sites are the anterior nasal mucosa and around the caruncle at the orifice of the lachrymal duct. First evident, as already noted, upon the second day of the disease, they increase in numbers during the remaining two or three days before the appearance of the exanthem. As the rash commences to appear Koplik's spots begin to fade, and usually by the time the rash is fully out are to be made out with difficulty or not at all.

A diagnosis of Koplik's spots is equivalent to a diagnosis of measles. The chief difficulty experienced by students lies in the realisation of their minute size. In infants and young children, especially during dentition when the buccal mucous membranes may be unhealthy, other lesions are frequently confused.

In the infant flakes of milk and the aphthous patches of thrush, both dead white in colour, comparatively huge in size, haphazard in distribution and detached with ease (Koplik's spots being detached only with difficulty), are sometimes

mistaken. In the older child dental ulcers, usually opposite a sharp or carious tooth, are yellow in colour and may attain the size of a lentil or larger. Needless to add, any of these conditions may coexist with Koplik's spots. Also, particularly in very young children, Koplik's spots may be masked by the pultaceous deposit—the erythemato-pultaceous stomatitis of Comby which is characteristic of measles, and sometimes indicative of a severe attack. Whether Koplik's spots are identified or not, a complete examination of the buccal cavity must be made.

Towards the end of the stage of the enanthem it is frequently possible to observe dull red blotches upon the soft palate, of similar character to those which compose the exanthem which will appear later.

The tonsils are congested and may present a yellow, amorphous, readily removable exudate.

The *tongue* in the early stages of measles is usually furred but moist. As the disease advances the fur strips, and it is important to note that at any rate as regards the anterior third the tongue in measles during the stage of the *exanthem* may closely resemble the clean red strawberry tongue of scarlet fever. Many cases of measles are misdiagnosed as scarlet fever owing to the occurrence in both diseases of the acute exfoliative glossitis due possibly in both cases to hæmolytic streptococci. Double infections of measles and scarlet fever are not uncommon.

II. *Stage of the Exanthem.*—After three or four days of coryza, cough and conjunctivitis, and sometimes, especially in infants, enteritis, the rash of measles commences to appear in the form of small dark red macules or maculo-papules (see Fig. 23). These lesions are first evident behind the ears and at the junction of the hairy scalp and forehead. Within a few hours every anatomical division of the body is invaded.

The macules of measles appear in crops, the face ordinarily being most densely covered. The effect of this cropping is such a profusion of lesions that, by confluence, blotches are formed, many of which tend to have a crescentic or thumb-nail edge. Thus although on its first appearance the eruption may consist of discrete macules, a few hours later the typical blotchy rash may be seen, especially upon the face and abdomen. The circum-oral area is invariably invaded. When the rash is fully erupted it tends to deepen in colour, and petechiæ may be evident. Thereafter the lesions fade, leaving as they do so faint pigmented areas (measles staining) of retrospective diagnostic utility. Lastly, branny desquamation occurs on

the face, trunk and limbs, including the palms and soles (*cf. rubella*).

Variations in the Eruption.—(i) The attack of measles may be confined to the enanthem: no rash appears, *morbilli sine*

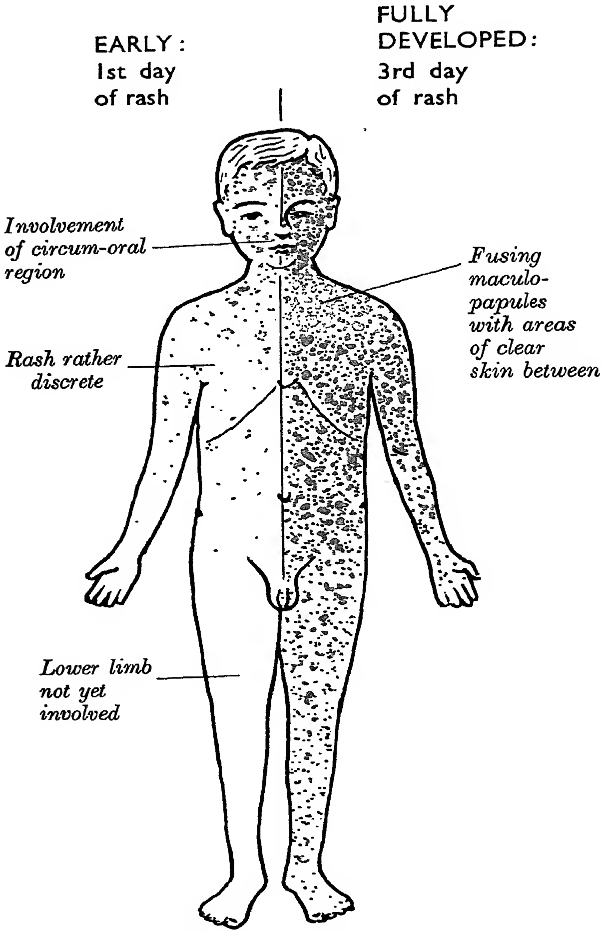


FIG. 23.—Diagram to show the Development of the Rash of Measles. Note that the face, including the circum-oral area, is invaded early and that the density of the rash is greatest upon the face and trunk.

morbillis (Sydenham). (ii) Mild, abortive, naturally or artificially modified or attenuated attacks, *formes frustes*, in which the lesions everywhere remain discrete macules or maculopapules, including the so-called papular measles. The colour of the lesions may not attain the typical robust dull red, the shade being pink rather than red. Failing the recognition —perhaps the occurrence—of Koplik's spots such cases may be confused with rubella. (iii) *Morbillus bullosi ;* a rare clinically severe variety in which some of the lesions become bullous. (iv) *Toxic and hæmorrhagic measles ;* the lesions, especially on the face, are raised and velvety to the touch, and dusky in colour ; petechiæ and ecchymoses are numerous. In *true* hæmorrhagic measles bleeding occurs not only into the skin but into the conjunctiva and from mucous membranes generally, and is almost invariably fatal ; it must not be confused with hæmorrhages into the lesions of the rash, which are not uncommon, merely indicate a severe exanthem and are associated subsequently with marked pigmentation or staining.

Prodromal Rashes.—It is important to remember the occasional appearance of prodromal rashes in measles. These are of two types : (i) a fleeting *scarlatiniform* rash of haphazard distribution and (ii) a faint *morbilliform* rash, also fleeting. Both disappear before the true eruption. The morbilliform prodromal rash may lead to a premature and disconcerting announcement that the measles rash has come and gone.

In the uncomplicated case the catarrhal manifestations, including pyrexia, abate as the rash fades. When this is complete and the temperature falls to normal, an uncomplicated attack, except for the resulting debility, is at an end.

Differential Diagnosis.—(*a*) *Pre-exanthem or Catarrhal Stage.* —The real nature of a suspected common cold and similar "influenzal" conditions, or the catarrhal stage of whooping-cough, is made clear by the identification of Koplik's spots (*vide supra*). (The prompt isolation of a child presenting any such condition, and a careful watch for Koplik's spots if they are not at once detected, are obvious precautionary measures whether the condition is in fact measles or not.)

(*b*) *Exanthem Stage.* — *Other Infectious Diseases.* — These include *rubella*, *scarlet fever*, *smallpox* and *paratyphoid fever*.

(i) The rash of *rubella* consists typically of pink discrete macules. It tends to appear first on the face but does not invariably do so, or having appeared may soon disappear. The concomitant catarrhal symptom and systemic disturbance in rubella are trifling : Koplik's spots never occur. Enlargement of the suboccipital group of glands is highly suggestive.

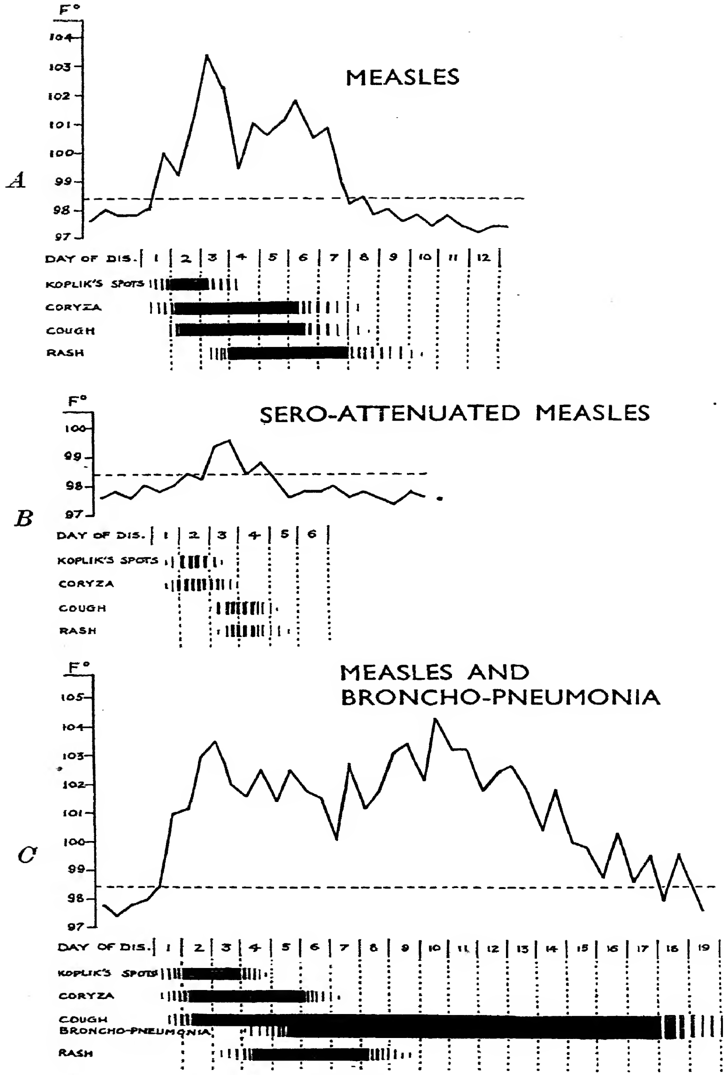


FIG. 24.—Charts showing Time of Onset, Duration and Intensity of the Chief Clinical Manifestations of: *A*, Measles (Uncomplicated); *B*, Sero-attenuated Measles; *C*, Measles complicated by Broncho-pneumonia.

(ii) It is not uncommon for the rash of *scarlet fever* to be coarse and blotchy on the limbs—particularly upon the outer aspects of the forearms, and partial examination of the skin picture may lead to confusion. A positive Schultz-Charlton test (*q.v.* Chapter XII) is pathognomonic of scarlet fever.

(iii) The eruption of *paratyphoid* may be profuse and occur as pinkish-brown maculo-papules on the forehead and face as well as at the more usual sites. It has been mistaken for measles. The longer prodromal illness, the character of the temperature chart, positive blood culture and Widal's reaction are diagnostic.

(iv) *Smallpox* may be at once excluded in a successfully vaccinated child, but in the unvaccinated and those whose immunity has lapsed with time, the prodromal illness of influenzal type, especially in *variola minor* (*q.v.* Chapter XXII), lasting some three days and followed by an eruption of maculo-papules or papules first on the forehead, may give rise to difficulty. After further observation, in isolation of course, the distribution and evolution of the lesions of smallpox become clear. It is to be noted, however, that in the most severe types of measles, as of smallpox, the lesions tend, especially on the forehead, to be velvety maculo-papules and that in smallpox of this type further evolution may be prevented by the death of the patient from toxæmia.

(v) *Drug Rashes.*—*Copaiba* and similar oleo-resins may give rise to a rash resembling measles. Except by accident, the drug is not likely to be given to a child. In this connection some of the proprietary "backache and kidney" pills must be borne in mind.

Although the salicylate rash is usually scarlatiniform, several instances of rashes of morbilliform type have been noted by us, following the self-administration by patients of abnormal doses of *aspirin* for influenza. The conjunction of fever and catarrh followed by an eruption—which, however, frequently spares the face—has led to a diagnosis of measles.

Among other drugs which may give rise to a morbilliform eruption are the sulphonamides, antipyrine, sulphonal, veronal and belladonna.

(vi) *Serum rashes* sometimes have a morbilliform element: the rash tends to be more dense at the site of injection, if this has been subcutaneous or intramuscular, and nearly always at some time during the period of eruption the typical wheals are to be discovered—whatever the route of injection.

(vii) *Food Rashes.*—Rashes due to the ingestion of certain

foods may in susceptible people give rise to rashes of morbilliform type associated or not with gastro-intestinal symptoms.

(vii) *Erythema multiforme* is occasionally misdiagnosed as measles.

(viii) The pigmented blotches which tend to appear more markedly on the abdomen, which are evidence of a faded measles rash, have in our experience been diagnosed as the eruption of exanthematic typhus, hæmorrhagic smallpox and cerebrospinal fever.

Complications.—From the clinical standpoint measles must be regarded as a combined virus and bacterial infection—the latter being, primarily at least, an upper respiratory tract infection, chiefly with strains of the hæmolytic streptococcus. The *virus* is concerned directly, or possibly in the rôle of activator of an existing virus, in one of the complications of measles, viz., *encephalitis* ; the remaining complications of the disease are caused by bacterial concomitants proliferating upon mucous membranes, the vitality of which has been damaged by the virus.

The buccal and post-nasal mucosa are dangerous reservoirs of secondary bacterial infection, and the younger the child the more dangerous are they likely to prove. Some of the complications arise from these foci by (i) direct spread of the organisms, (ii) ingestion or (iii) aspiration of mucopus. Thus, direct spread from a focus in the post-nasal space along the Eustachian tube gives rise to otitis media ; ingestion of mucopus from the same source to gastro-enteritis or enteritis ; and aspiration to broncho-pneumonia. For purposes of clinical description, however, the complications of measles are more conveniently considered under the headings of the systems and special senses affected.

1. **Respiratory.**—(*a*) *Laryngitis.*—Slight hoarseness which denotes catarrhal laryngitis may be regarded as normal during the prodromal stage, and a moderate increase as the stage of eruption is approached need cause no anxiety, but occasionally this prodromal laryngitis becomes obstructive and alarming : inspiratory stridor, recession and cyanosis may suggest the advisability of operative relief—intubation or tracheotomy—but such measures, if concomitant laryngeal diphtheria can be excluded, are best avoided since, almost invariably, the condition improves as the rash appears. Intubation, owing to the congestion of the mucosa, is difficult and by no means devoid of the danger of producing œdema of the glottis, and tracheotomy is very liable to be followed by fatal broncho-pneumonia.

In some cases laryngitis persists throughout the attack of measles and into convalescence. Since the condition is probably ulcerative and may produce stenosis, the early advice of a laryngologist should be sought. Laryngeal diphtheria may occur at any stage of the attack of measles.

(*b*) *Tracheitis* of transient catarrhal type is not unusual as an extension of laryngitis.

(*c*) *Pneumonia.*—Broncho-pneumonia (*vide* Chapter VI) is the outstanding complication of measles. Lobar pneumonia is less common and, as is generally the case in children, less fatal. In a consecutive series of 1,404 children up to the age of five years admitted to hospital with measles over a period of nine months, the incidence of broncho-pneumonia on admission or within the ensuing two or three days was 12·3 per cent. with a case fatality rate of 30 per cent. Among a small group of infants aged *less* than six months, most of whom, it is noteworthy, suffered naturally modified attacks of measles, there was no instance of broncho-pneumonia. The incidence of this complication among those of from six to twelve months was 17·5 per cent. with a fatality rate of 51·4 per cent. Among those from one to two years the incidence was 17·3 per cent. with a fatality rate of 36·2 per cent. Compared with those of children up to one year of age, the incidence and fatality rates of broncho-pneumonia among those from two to five years of age were both approximately halved. Over the age of five the incidence and fatality were negligible.

In the same series broncho-pneumonia of late onset (second week of measles and onwards) occurred in 2·6 per cent. The fatality rate was 28 per cent. With one exception the deaths occurred exclusively among those aged from six months to two years (Harries, 1935). Kohn and Koiransky (1929) have produced radiological evidence to show that peri-bronchial infiltration occurs in every case of measles, mild or severe. Coveney and Dixon (1938) from radiological examination of measles patients who had recovered from broncho-pneumonia concluded that in every case there is residual damage. Whether this damage is permanent in every instance or is repaired in the course of time is yet to be shown, but there can be little doubt that broncho-pneumonia during an attack of measles may be the starting-point of fibroid lung and bronchiectasis. *Empyema* may occur in association with either broncho or lobar pneumonia.

2. **Gastro-intestinal.**—(i) *Ulcerative Stomatitis.*—The early erythemato-pultaceous stomatitis of Comby has already been mentioned. This condition, given proper attention to the

mouth, usually clears up in a few days, but in any case of measles if the hygiene of the mouth is neglected a rapidly progressive ulcerative stomatitis terminating fatally from broncho-pneumonia and septic absorption may arise.

(ii) *Cancrum Oris.*—This very fatal complication, confined to neglected and debilitated children, is now rarely encountered. In most cases it is probable that the Plaut-Vincent symbiosis of spirochæte and fusiform bacillus (*vide* Chapter XIV, Fuso-spirillosis) is responsible. Commencing as a small ulcer upon the buccal mucous membrane, the condition advances rapidly: the mucous membrane is undermined and the cheek may be perforated. Extensive sloughing and necrosis of the tissues may result, if the child survives sufficiently long, with exposure of the jaws and teeth. The same rapid necrotic destruction may involve the vulva and is then known as *noma.*

Unless the condition is discovered early and vigorously treated, recovery rarely occurs. So far as possible the diseased tissue should be removed by scraping and some application such as phenol or nitric acid applied. Combined with this local treatment an injection of one of the arsphenamine preparations should be given (*vide* Chapter XIV, Fuso-spirillosis). Goodall (1930) records a case of cancrum oris following whooping-cough. The child recovered: several years later the defect in the cheek was repaired by a plastic operation, and more recently plastic operations have proved successful in other cases.

(iii) *Gastro-enteritis* and *enteritis* (*vide* Chapter XXVIII), the incidence of which is almost confined to children up to two years of age, may occur during the prodromal stage, or later in the attack when the rash is fully developed. It may also occur during convalescence. In the series already referred to an intestinal tract infection occurred as an early complication in 1·5 per cent. of all children up to five years of age. The fatality rate was 33·3 per cent., although it must be added that broncho-pneumonia was also present in most of the fatal cases.

It must be remembered that *dysentery*, usually of Sonne type (see Chapter XXIX, Dysentery), may be mistaken for the enteritis of measles. Careful inspection and bacteriological examination of the stools is called for in any case of diarrhœa complicating measles. *The prompt isolation or barrier-nursing of the child is in any case essential.*

3. **Central Nervous System.**—Ford (1928) estimates the frequency of involvement of the nervous system in measles at 0·4 per cent.

Convulsions and *delirium* and a *meningeal reaction* may be

associated with the toxæmia of measles or with the onset of broncho-pneumonia or apical pneumonia.

The occurrence of measles-meningitis as distinct from *bacterial meningitis* (usually streptococcal and otogenic) has been recorded, but it is probable that such cases are manifestations of meningo-encephalitis.

Encephalitis or *meningo-encephalitis* is the typical and outstanding nervous complication of measles. The pathogenesis is believed to be similar to that of the encephalitis complicating other acute specific infections such as vaccinia and varicella. The symptoms are usually first noted when the temperature has returned to normal and the rash has begun to fade, although they may appear at the height of the attack of measles, or rarely in the prodromal period (Ford). There is no doubt that some examples of measles-encephalitis are so mild and transient as to pass unnoticed unless the child is under careful and constant observation, but the onset is usually sudden and well marked. The temperature rises sharply and the child, if old enough, may complain of headache. In very young children convulsions may occur.

The mentality of the child changes : it may be irritable or become delirious, but more usually is drowsy and later stuporose. Twitchings and myoclonus are characteristic, and there may be evidence of meningeal irritation. The attack may terminate completely after a few days of unconsciousness, or this may persist and ultimately be followed by residual damage, among which Ford enumerates as common are spastic paralysis, ataxia, tremors, choreic and athetoid movements, myoclonus and aphasias. Mitman *et al.* (1937) stress the frequency of meningeal signs and the diagnostic importance of involvement of the sphincter of the bladder. The cerebrospinal fluid is usually under increased pressure : the lymphocytes, particularly monocytes, are moderately increased ; sugar is variable—it may be normal, increased or diminished. There is some increase in the protein content.

Neal and Appelbaum record a series of 12 cases : 3 died, and 6 of 9 who were followed up made a complete recovery. Mitman records the successful use of serum derived from a patient recovered from measles encephalitis.

4. **Special Senses.**—(*a*) *Ear.*—Infection of the middle ear, usually with the hæmolytic streptococcus, may occur at any stage of measles—but does not necessarily result in perforation and discharge. Systematic examination of the drum heads in an unselected series of 400 measles patients by Linford (1935) in the wards of the North Eastern Hospital showed that in a

quarter of the cases the ears remained normal throughout : in half there occurred mild otitis which varied from injection of the tympanic membrane head to the pale full drum of a catarrhal otitis media. In the remaining quarter the otitis was severe and resulted in perforation and otorrhœa. In the series of measles cases from the same wards already referred to (Harries, 1935), suppurative otitis media occurred in the early stages of the attack of measles in 7 per cent. of all cases up to the age of five and late in the attack in 8·6 per cent.—a total incidence of 15·6 per cent. up to the age of five. The maximum incidence fell upon children up to the age of three.

Linford found that in an unselected series of 100 cases of suppurative otitis media no less than 24 had a definite history or clinical evidence of previous infection of the ear. Thus in many cases of measles the occurrence of otitis media is really due to the reinfection of ears already damaged. In 44 there were associated conditions of the upper respiratory or respiratory tracts. The commonest site of perforation (unilateral or bilateral) was anterior-superior.

The duration of otorrhœa in 98 cases varied from under one week (16 cases) to over six weeks (23 cases). Mastoiditis occurred in 5 of the series of 100.

The most important principles in the *treatment* of otitis media are (i) segregation of the patient to minimise the risk of reinfection, (ii) repeated mopping of the ear under direct vision through the auriscope, (iii) the simultaneous treatment of nasal discharge which Linford found in her series to have a definite influence on the persistence of the discharge and on the end-result, (iv) the continuance of treatment until the ear is dry—preferably with the perforation healed. Primary paracentesis is rarely possible (*vide* Chapter VI).

(*b*) *Eye.*—*Conjunctivitis* and *photophobia* may be regarded as normal concomitants of the prodromal stage. Marginal blepharitis may occur early and persist throughout the attack. The outstanding ocular complication is *corneal ulcer* which may be bilateral. Unless promptly diagnosed and adequately treated, the ulcer deepens rapidly and perforates, resulting in total destruction of the globe. Sympathetic panophthalmitis may ensue. In all cases of measles systematic nursing attention to the eyes and lids should be given from the earliest stage. At the first sign of corneal involvement, atropine drops should be instilled and frequent irrigation with boracic lotion from an undine carried out. Silver preparations should be avoided. After irrigation *dilute* yellow oxide mercury ointment may be introduced.

The foregoing measures must be regarded as tentative. *Expert ophthalmic advice should be sought at the slightest sign of advance of ulceration.* At best a nebula which if central may obscure vision will remain ; at worst, blindness.

The occasional occurrence of *diphtheritic conjunctivitis* must be borne in mind (*vide* Chapter XIII, p. 157). If there is any suspicion of this, diphtheria antitoxin must be injected at once ; swabbing and virulence tests are to be considered as confirmatory only.

(*c*) *Skin.*—*Impetigo* in the neglected child and *furunculosis* during convalescence may be troublesome. *Pemphigus* may, as Ronaldson (1937) points out, be associated with measles but must be distinguished from pemphigus with a morbilliform eruption and from morbillus bullosi (*vide supra,* p. 205). *Purpura* is an uncommon condition. Laurent (1933) records a case which occurred during convalescence ; cure followed injection of the mother's fresh citrated blood.

Prophylaxis—

1. **General Measures.**—(*a*) *Notification.*—Statutory notification of measles has not upon the whole proved successful : the disease is not included in the Public Health Act, 1936. Various methods of informing the health authority are practised with a view not only or mainly to the isolation of the declared case but to the supervision of contacts. Thus the first case occurring in a family is sometimes made notifiable as in London. The main agents, however, are school teachers and school nurses in liaison through the medical officer of health with health visitors. School closure is not now favoured. Exclusion of children suffering from measles is, of course, essential, but the exclusion of healthy home contacts, provided arrangements can be made for their daily examination, is not now practised in London. It has been found that the children are better at school than playing in the streets, and, moreover, earlier information as to the onset of measles is thus obtainable.

If *quarantine* is imposed upon non-immunes it should be for sixteen days ; seventeen days if seroprophylaxis (*q.v.*) has been practised.

(*b*) *Isolation.*—Isolation, to be effective, must be carried out early in the catarrhal stage. Infectivity wanes as the rash appears, and when this has faded has ceased. It is not maintained by complications. Twelve to fourteen days' isolation is ample. Concurrent disinfection is important. " Spring-cleaning " suffices for terminal disinfection.

(*c*) *Hospitalisation.*—The admission to hospital of children suffering from measles is not *qua* measles, a preventive measure.

By the time the rash has appeared the contacts have been infected. Hospitalisation is frankly a social and curative measure, but even so is only justifiable under proper conditions of spacing and nursing. The overcrowded measles ward is more lethal than the overcrowded tenement; broncho-pneumonia thus kills not only the child admitted for this complication but a considerable proportion of his ward-mates. It is idle to contend, however, that the slum child suffering from measles is not infinitely better off if removed to an airy, well-spaced ward where he can receive skilled nursing under good conditions (*vide* successive L.C.C. Reports on Measles Epidemics).

(*d*) **Seroprophylaxis.**—Attempts have been made to prepare measles immune sera from animals. So far these animal antisera have proved of no value. Nicolle and Conseil (1918) showed that about a week after the temperature has returned to normal the blood of the measles patient contains specific protective antibodies. With some decline in potency these antibodies remain for life. Blood serum from *convalescents* or from *adult immunes*, *placental extracts* or *parental whole blood* injected into exposed non-immunes will (1) confer temporary passive immunity (sero-prevention), or (2) confer such a measure of partial passive immunity as to secure a miniature, attenuated attack of measles (sero-attenuation), and, provided it be not attenuated *too* greatly, result in solid active immunity.

Both these measures have their particular uses. Thus if the exposed susceptible child is already ill or in poor health, the hazards even of an attenuated attack may be too great, and temporary *prevention* is the method of choice. If the exposed child is healthy, then clearly an *attenuated* attack is not only permissible but desirable.

Measles immune serum is prepared from the blood of a number of suitable donors and pooled. Before pooling, individual samples must be shown to be Wassermann negative and the donors must be otherwise healthy.

Blood from convalescents should be collected about the fourteenth day after the onset of the attack. Adult immune donors must be young, and preferably not longer than ten years should have elapsed since the attack of measles. The adult donor should yield 250 to 300 c.c. of blood: the resulting volume of serum is about half this.

For the technique of collection and preparation, see McCartney (1933) (L.C.C. Report on Measles Epidemic, 1931-32).

Since pooled samples of serum vary in protective powers and there is no method of titration, dosage at present is empirical.

For *prevention*, serum must be injected not later than the fifth day after exposure; for *attenuation* between the sixth and ninth day. Serum injected later than the ninth day has no prophylactic effect. Around the site of injection the rash may fail to appear. This is the *Debré extinction sign*: its appearance is of practical value as evidence that the sample possesses protective properties.

Gunn (1933) has shown that half the *preventive* dose injected within the first five days will *attenuate* the attack, thus effecting a considerable saving in serum, which is never easy to obtain in other than limited supply. For this reason also the stock of serum should ordinarily be reserved for children under four years of age. The serum must be stored in an ice-chest. Adult immune serum should be injected in double the dose of convalescent serum. The following scheme is suggested for children under five years of age:—

Serum	Days after Exposure		
	One to Five		Six to Nine
	Prevention	*Attenuation*	*Attenuation Only*
Convalescent .	5 c.c.	2·5 c.c.	5 c.c.
Adult immune .	10 ,,	5·0 ,,	10 ,,

Over the age of five years inject double these doses.

Gunn regards the dose of serum for children under three years as the standard dose. He assesses the dose of convalescent serum for older children by multiplying the age in years by four. Of adult serum he recommends a flat dose of 10 c.c. as being as effective as an age-adjusted dose.

Placental Extract (Immune Globulin).—Placental extract (immune globulin) in lieu of serum for the prophylaxis of measles was first used by M'Khann and Chu (1933), and promising results have been recorded by a number of workers. The extract is obtained from the placentas of white women with negative Wassermann and Kahn tests; and the cord-

blood must also give a negative Wassermann reaction. By suitable methods, the globulin fraction to which the protective principle adheres is at once retained and preserved with phenol. The advantages of placental extract are (i) the abundant source of supply, (ii) the small dosage: 2 c.c. for attenuation, 3 to 4 c.c. for prevention. There has been one disadvantage which will doubtless be overcome—the liability to produce reactions which have been held to be due to tissue proteins.

Parental Whole Blood.—For the protection of familial contacts, whole blood obtained from an immune parent may be injected into the buttock: the same syringe being employed. For children under five years of age a dose of 30 c.c. (half into each buttock) is recommended for *attenuation.* The main disadvantages are the bulk of the injection and the development of an artificial hæmatoma.

Clinical Aspects of Attenuated Measles.—1. A prolonged incubation period is common: fourteen or more days to the commencement of the catarrhal stage.

2. Slight pyrexia, slight catarrh, Koplik's spots inconstant, rash sparse, discrete and usually pink, resembling that of rubella.

3. No complications.

It must be remembered that a child with attenuated measles is nevertheless *infective.*

Treatment.—1. *General.*—An abundance of fresh air is essential; many children die as the result of a stuffy, airless room. In wards a minimum of 12 ft. between cot-centres must be maintained. Parallel-spaced cots under open windows are very satisfactory. The child with broncho-pneumonia is preferably nursed on a balcony, precautions not against fresh air but against cold and wet being taken.

The diet should be as generous as the child's general condition permits; milk and milky foods during the pyrexial stage, minced meat, fish and green vegetables, fresh fruit and custards as soon as the temperature has dropped.

2. *Therapy.*—(*a*) *Drugs.*—There is no specific drug. Amidopyrine (pyramidon), at one time advocated, is not only without value but not free from danger. The old-fashioned Dover's powder (*pulv. ipecac. et opii,* B.P.) during the early stages checks the cough, induces action of the skin and secures sleep. Thompson and Greenfield (1938) have found the sulphonamide group of drugs of value in the prevention and treatment of complications, especially broncho-pneumonia and otitis media. Prontosil album was given early in a daily prophylactic dose of 0·5 gm. for children up to the age of one

year and a daily treatment dose of 0·75 gm. with a proportionate increase for age up to 2 gm. for prophylaxis, and 2·5 gm. for treatment in the ten to fifteen year group. The prophylactic dose was given for ten days and then reduced by a third or a half. The treatment dose, for existing complications, was maintained until effective and then reduced similarly until the discharge of the patient.

As regards prophylaxis, broncho-pneumonia occurred in 1·7 per cent. of those receiving the prophylactic dose, as compared with 4·8 per cent. of the controls. Of those treated for broncho-pneumonia 11·1 per cent. died, compared with 28·7 per cent. of the controls. Comparable success was obtained in the prophylaxis and treatment of otitis media.

(*b*) *Immune Serum.*—Claims made for human-immune serum in the *therapy* of measles have not been substantiated. Occasionally an intramuscular injection of parental whole blood will turn the scale in broncho-pneumonia, due, probably, to the supply of complement (*vide* Chapter VI, *section* Broncho-pneumonia).

Other complications must be treated as they arise.

SUMMARY OF CHAPTER XVI

Clinical Stages : (i) Prodromal *catarrhal* : Coryza, conjunctivitis, cough, Koplik's spots, pyrexia.
(ii) *Rash :* blotchy, dull-red maculo-papules, generalised (fourth day).

Chief Complications : Broncho-pneumonia, enteritis, otitis media.

Prophylaxis : Sero-prevention and sero-attenuation.

Treatment : Symptomatic ; sulphonamides for broncho-pneumonia and otitis media.

CHAPTER XVII

RUBELLA

(German Measles ; *Röteln* ; Rubeola)

DEFINITION.—Rubella is characterised by slight catarrhal symptoms, palpable enlargement of the sub-occipital lymphatic glands and a rash composed of pink macules which may become locally or generally confluent. The incubation period is long : the illness short and trivial.

Ætiology.—The causal agent, which is quite distinct from that of measles, is believed to be a filterable virus. Rubella is classed by Glanzmann with glandular fever (*vide* Chapter XX) as a benign infective lymphoblastosis.

The disease is endemic in large cities. At somewhat irregular intervals localised epidemics occur which attain their peak in the spring and early summer. Owing to the lesser infectivity of the virus, or more probably to the relative slightness of the catarrhal stage, epidemics of rubella never reach dimensions comparable with those of measles. Occasionally epidemics of rubella and of measles or scarlet fever coincide or overlap and add to the difficulties of diagnosis.

Although under conditions of intimate and repeated exposure, outbreaks among young children may occur, rubella ordinarily tends to attack older children and adolescents.

With the rarest exceptions, deaths ascribed to rubella are caused by intercurrent conditions. The naked eye pathological changes in rubella, if such occur, are unknown.

Blood Picture.—The characteristic blood picture occurs late. The neutrophils are reduced early, but lymphocytosis and monocytosis are seen only when the rash is fading and typically, but not constantly, there is a considerable increase in Türck or plasma cells.

Incubation Period.—This ranges from fourteen to nineteen days. Periods of **seventeen or eighteen** days are very common.

Clinical Features.—*Invasion.*—The prodromal symptoms of rubella ordinarily consist in slight general malaise, headache and pains in the limbs, followed in a few hours by catarrhal symptoms and conjunctivitis which persist during the appear-

ance of the rash and decline *pari passu* as it fades. The temperature is moderately raised at the onset (99° to 101° F.) and reaches normal again in about three days. In young children, prodromata may be clinically inappreciable, the first event to be noted being a rash. In adults, however, the prodromata may be quite severe, with considerable malaise and complaint of stiffness of the neck (this is somewhat characteristic) and sore throat.

The Enanthem.—There is usually to be noted slight general injection of the faucial mucosa. Tonsillar or faucial exudate is uncommon.

Koplik's spots *never* occur in rubella. Forchheimer described small papules as occurring on the soft palate in the early stages of rubella. We have observed, very inconstantly, small deep pink maculo-papules on the soft palate. These might possibly have been Forchheimer's spots: they were similar in appearance and probably identical in nature with the lesions of the exanthem which appear later. It is to be noted that in *measles*, dull red blotches on the soft palate are not uncommonly noted during the stage of the enanthem and that in *scarlet fever* the soft palate presents typically a punctate or stippled appearance.

Lymphadenitis.—The occurrence of lymphadenitis is very constant in rubella, but the time of onset is variable. The glands most commonly enlarged are those of the suboccipital groups; occasionally, the epitrochlear and popliteal glands are also involved. The glands are *palpably*, rarely visibly, enlarged sometimes before the appearance of the exanthem, but are more commonly noted when the rash has partially or wholly erupted—probably because it is only then that the disease is suspected. The enlargement of the glands subsides within a day or two. In adults they may be tender on pressure. Suppuration never occurs. The *spleen* may be enlarged to percussion, and occasionally to palpation, during the early stages of rubella.

The Exanthem.—The rash usually appears in twenty-four hours or less after the initial symptoms. The primary lesion is a small macule definitely *pink* in colour. These macules may—

(i) Remain discrete throughout;
(ii) Coalesce locally into pink blotches which lack the robust appearance and crescentic edges of the similar blotches in measles; or
(iii) The blotches may themselves coalesce, particularly on the trunk, giving rise to considerable areas of erythema of scarlatiniform type (*vide infra* Diagnosis).

A tendency for the rash to appear on one anatomical division of the body and then wholly or partly to fade before erupting elsewhere is characteristic of rubella. This results in the skin picture being bright in some areas and faded in others, but not with the regular gradation of fading from above downwards which is seen in scarlet fever and to a lesser degree in measles.

The common order of appearance is—

(i) Face ; (ii) trunk ; and (iii) limbs.

The rash on the *face* appears first behind the ears and upon the forehead. It invades the circum-oral area, although sometimes very sparsely.

Commonly, the rash after appearing on the *face* fades rapidly, but it is to be noted that it may persist on the face throughout ; may be confined to the face ; or may never invade the face at all.

On the *trunk* the rash tends to be more profuse than elsewhere, and, as already mentioned, may by confluence of the lesions present erythematous areas of considerable extent. These areas are *pink* and *not* punctate.

On the *limbs* the rash is usually sparse, the lesions remaining discrete. Owing to this and to the fact that the limbs are usually the last sites to be invaded, it is frequently possible to see typical recent lesions on the dorsum of the foot and the adductor surface of the thigh, when the rash elsewhere has become confluent or has faded.

As noted by Trousseau, the rash of rubella may give rise to *itching*. This phenomenon is not constant ; in our experience it occurs more frequently in adults. Pruritus, especially in adults, may be important in differentiating the roseolar rash of secondary syphilis (*vide infra* Differential Diagnosis).

The rash usually persists for two or three days and then with the catarrhal symptoms disappears without leaving the staining or mottling frequently observed in measles ; but the rash may fade completely within twenty-four hours of its eruption. Scanty branny desquamation may be observed after a profuse rash, but does not occur on the palms or soles.

Relapse in rubella does not occur. *Second attacks* are very rare. Some at least are of doubtful authenticity.

Differential Diagnosis.—It is necessary to distinguish rubella from (1) measles, (2) scarlet fever, (3) glandular fever, (4) secondary syphilis, (5) pityriasis rosea, (6) food or drug rashes, (7) serum rashes. The conditions most usually confused, since they are common and frequently concurrently epidemic, are

measles and scarlet fever: it is of the utmost importance to exclude secondary syphilis.

1. *Measles.*—The incubation period to the earliest catarrhal symptoms, which are much more marked, is shorter than that of rubella. The pre-exanthem phase in measles lasts three or four and sometimes five days. Sneezing and photophobia are characteristic; the presence of Koplik's spots is pathognomonic of measles. The child with measles is miserable, but with rubella unconcerned. In measles the temperature frequently rises sharply to 103° or 104° F.; it remains raised until the rash begins to fade. The macules of measles, dull red in colour, erupt in a definite order from above downwards, and there is a much greater tendency to form blotches with crescentic margins. The rash of measles does not entirely disappear from any site, but fades, after complete eruption, in the same order as which it appeared. Intense measles rashes are commonly accompanied with petechiæ or linear ecchymoses particularly upon the abdomen, and, in this situation especially, temporary pigmentation which is quite characteristic, may result. Marked branny desquamation, involving also the palms and soles, is common. It may be virtually impossible to distinguish measles artificially attenuated by human immune serum from rubella, unless Koplik's spots can be identified. A previous history of one or other disease given by the parents must ordinarily be regarded as quite unreliable.

2. *Scarlet Fever.*—The following points are of assistance: the short incubation period and abrupt onset with pyrexia, which, however, may be only slight; disproportional tachycardia, sore throat, headache and vomiting; marked injection of fauces, possibly tonsillar exudate; stippled appearance of soft palate; simple flush on cheeks; circum-oral pallor. The rash proper appears on neck and thence downwards; red, punctate; minute petechiæ on limb flexures (Pastia's sign). The Schultz-Charlton test is likely to be positive. A smear from the throat plated on blood agar and incubated overnight almost invariably gives a pure culture of hæmolytic streptococci, diagnosed by zones of hæmolysis around the colonies.

3. *Glandular Fever* (Infective Mononucleosis).—Rashes of any description are rare, but roseolar eruptions have been recorded. In glandular fever some days of malaise precede the lymphadenitis which affects first, most commonly, the glands behind the sternomastoid; they become *palpable and visible*, some attaining the size of plums; the spleen is palpable in half the cases. The blood picture of glandular fever shows

considerable numbers of monocytes with a bi-lobed nucleus which stains poorly (see Chapter XX).

4. *Secondary Syphilis.*—A roseolar rash is common, together with polyadenitis in secondary syphilis. The syphilitic eruption avoids the face and may be profuse not only on the trunk but on the flexor surfaces of the limbs: the distribution is symmetrical. The eruption is much more persistent than that of rubella and as it fades tends to assume a lilac tint and to leave coppery staining. The rash does *not* itch. Symmetrical snail-track ulcers on the fauces, anæmia, possibly alopecia and evidence of a primary sore are other important diagnostic points. The Wassermann reaction is positive.

5. *Pityriasis Rosea.*—The lesions are dimorphic and consist of (i) small pink macules of irregular shape and varying size, and (ii) larger oval plaques the size of a penny; originally pink, the centre fades to a fawn colour, the epidermal edge may be raised—usually a large "herald patch" may be found on the trunk. There are no catarrhal symptoms, but lymphadenitis may occur. The eruption may persist for many weeks.

6. *Toxic Rashes* due to food or drugs when of macular type are usually of a robust red colour and of irregular distribution. A history is frequently forthcoming. There is a moderate increase in neutrophils.

7. *Serum Rashes.*—The typical lesion is a *wheal*, but there may be associated coarse morbilliform lesions: these are deep pink or red. Although the distribution may be generalised, serum rashes are usually more profuse at the site of injection. The "wandering" nature of the eruption, the intense pruritus and its control by adrenalin are additional points. Adenitis may occur but is not common.

Complications are of great rarity:—

1. *Encephalitis or meningo-encephalitis* has been recorded in recent years, usually in children under the age of fifteen. As in measles-encephalitis there appears to be a tendency to association with particular epidemics of rubella. Briggs (1935) finds that on the average encephalitis occurs from two to six days after the appearance of the rash. Fatality is very rare, complete recovery being the rule. From time to time nervous lesions such as Landry's paralysis have been recorded; some are probably fortuitous.
2. *Purpura Hæmorrhagica.*—Two examples have been

recorded, the first by Pitten (1929) and the second by Gunn (1933). In both, purpura occurred after the rash had faded and in both there was thrombocytopenia, normal plasma calcium content and prolonged bleeding time.

Prophylaxis.—*Isolation.*—The infectivity of rubella is of short duration and has ceased by the time the rash has faded. Five to six days' isolation are sufficient. Concurrent disinfection or destruction of articles soiled by the patient is important. Quarantine of contacts, if imposed, must extend to twenty-one days.

Treatment is simple: bed, a saline purge and light diet until the temperature has fallen. "Convalescence" is synonymous with recovery.

SUMMARY OF CHAPTER XVII

Clinical Manifestations: Slight catarrh, enlargement of external groups of lymphatic glands and a rash—pink macules which may become confluent.

Complications are rare: fatalities still more so.

Differential diagnosis from measles, scarlet fever, glandular fever, secondary syphilis, skin diseases, food, drug and serum rashes.

CHAPTER XVIII

SOME MINOR EXANTHEMATA

THE following conditions must receive brief mention :—

1. **The " Fourth Disease "** (*Dukes' or Filatow-Dukes' Disease*).—As described, this condition shares some of the characters of rubella and scarlet fever. Thus, a long incubation period ; few or no prodromata ; tonsillitis and a strawberry tongue ; a pink macular rash appearing first on the face (but avoiding the circum-oral area) and then spreading generally ; heavy desquamation ; the frequent occurrence of adenitis and albuminuria.

Opinion is divided as to whether this condition was an aberrant type of rubella or of scarlet fever ; it is all but unanimous that it was one or the other and not a separate clinical entity.

2. **Erythema Infectiosum** (*the " Fifth Disease "*).—This is one of several names for a condition first described by Tschamer as " örtliche Rötheln " (local rubella). On the Continent and in the United States epidemics have been recorded, but in this country only sporadic cases of a closely similar, possibly identical, condition have been encountered. Malaise, sore throat and catarrh are inconstant prodromata : the rash appears first upon the face as rose-red macules which become confluent on the cheeks. These confluent patches are defined above by the malar bones and medially by the nasolabial folds. They may be bridged across the nose. Circum-oral pallor has been noted. Later the rash appears upon the trunk and limbs. The facial lesions fade in a few days ; those on the trunk may persist for more than a week. Typically, over the areas of the faded lesions a violaceous tint is seen—particularly evident upon the face. There is no desquamation ; no adenitis ; no complications or sequelæ.

The blood picture is equivocal. Lawton and Smith (1931) record " a tendency towards eosinophilia and a relative lymphocytosis."

3. **Exanthema Subitum** (*the so-called " Sixth Disease "*).—Under this title the condition was described by Veeder and Hempelmann (1921). It is also known as " roseola infantum "

(Zahorsky) and "three days fever" (Glanzmann)—not to be confused with sandfly fever which is also known as three-day fever. The syndrome, which appears to be confined to infants up to two years of age, presents the following features :—

(i) Abrupt pyrexia (103° to 104° F.) *without* prodromata.
(ii) General "misery" of the infant.
(iii) Nasopharyngeal catarrh—described by Faber and Dickey (1927) but denied by most observers.
(iv) The pyrexia lasts for three days or so and *after* the temperature has dropped a rash appears on the shoulders and back, spreads to the abdomen, and lastly invades the face and limbs. More usually the rash, composed of small pink macules of irregular outline, resembles that of rubella rather than that of measles. Local confluence may occur. The eruption does *not* itch : it fades in forty-eight hours without pigmentation or desquamation.

The illness, such as it is, is confined to the three-day febrile stage ; by the time the rash appears the infant's general condition has returned to normal. The blood picture *may* assist diagnosis : there is leucopenia with relative lymphocytosis and monocytosis. Infectivity is very slight.

CHAPTER XIX

MUMPS

(Epidemic Parotitis)

DEFINITION.—Mumps, or epidemic parotitis, is characterised by temporary enlargement of the parotid, and sometimes other salivary glands, and by the occurrence of metastases of which orchitis is the most common.

Ætiology.—Mumps occurs all over the world. In civilised countries the disease is endemic, but localised epidemics occur. In children's institutions and schools outbreaks are not uncommon. The occurrence of mumps is independent of climate. *Seasonal prevalence* is marked ; most cases occur in spring, fewest in late summer.

Age Incidence.—The disease chiefly attacks children of school age, *i.e.*, those from five to fifteen years, and young adults such as army recruits living in dormitories or barracks. Children of pre-school age are rarely affected. There is no difference in *sex-incidence*, but owing to the occurrence of orchitis (*q.v.*) at and above the age of puberty, it must be regarded as a more serious disease in males than in females.

The *fatality rate* from mumps is negligible. A few deaths, chiefly of children, are recorded yearly in England and Wales, but it is probable that the actual cause is usually some concurrent condition. Passa (1935) states that during the years 1921-30 there occurred in the French army 90,054 cases of mumps ; of these, only 6 were fatal—a fatality rate of 1 in 15,000. Amongst the causes of death which may be ascribed to the disease itself are meningo-encephalitis, pancreatitis and œdema of the glottis. *Second attacks* are of extreme rarity.

The *causal agent* of mumps is a *filterable virus*. The early work of Mervyn Gordon in 1913 has recently been confirmed by Johnson and Goodpasture (1934), who reproduced the disease in monkeys by the inoculation of saliva. The virus exhibits *neurotropism*, and there is experimental evidence to show that its primary localisation is in the central nervous system, the glandular manifestations being metastatic.

Mode of Spread.—Mumps is spread by droplets of saliva or nasal secretion or by articles so contaminated. Some believe that the disease is infectious at the end of the incubation period before clinical signs are manifest. Missed cases of abortive type or unusual localisation, such as sublingual mumps, are also responsible for maintaining the chain of infection.

Pathology.—The virus of mumps affects almost, if not entirely, the peritubular or interstitial portion of the salivary glands. Several observers have been unable to detect any appreciable alteration in the character of the saliva, although secretion is temporarily decreased, from which it would appear that epithelial elements of the glands are unaffected. Suppuration of the glands does not occur unless the ducts are secondarily infected.

To explain the frequency of orchitis, many have held that there is an affinity between the parotids and the testicles. Probably more would agree with Trousseau's opinion that the orchitis is metastatic (blood borne) in evidence of this affinity. There is a definite relationship between mumps orchitis and sexual activity. Either the epididymis or the body of the testicle, or both, may be involved in mumps-orchitis, the essential pathological process, according to A. Stengel, jun. (1936), being a parenchymatous sclerosis. Atrophy of the testes, as the result of pressure necrosis, is stated to occur in some 60 per cent. of cases of orchitis, but although the organ may remain permanently diminished in size, function is not necessarily entirely lost. There may be temporary *splenomegaly*.

Blood Picture.—For so common a disease there is an extraordinary conflict of opinion about the blood picture. Most observers agree, however, that there is lymphocytosis with relative monocytosis. There is a similar disparity of statement as to the blood changes at the onset of orchitis, but here again it may be accepted that there is usually an increase of lymphocytes at the onset of this complication, although according to Feiling (1914), orchitis may not affect the blood picture.

Incubation Period.—The incubation period of mumps is most commonly **seventeen** to **eighteen** days, although periods as short as three days or as long as twenty-eight to thirty days have been recorded. These exceptional periods in this, as in other of the acute specific infections, always suggest the possibility of a "missed case."

Clinical Features.—*Onset.*—Although attention may first be called to the swollen face, there is usually a prodromal

period characterised by moderate pyrexia (100° to 103° F.), sore throat, furred tongue, constipation and possibly albuminuria. The pulse may be slow. Stiffness of the neck is a common complaint in adults. Epistaxis sometimes occurs. This prodromal stage may last for as long as four days before local signs appear. The onset is not always insidious: the disease may commence with a rigor or convulsion, or with a meningeal reaction—the so-called "cerebral mumps," of which many instances occurred among troops in the Great War.

If, as in an institutional outbreak, further cases are anticipated, it is possible to elicit two early signs before visible enlargement of the parotid gland occurs. These are: (1) Reddening of the papilla of Stensen's duct on both, or more commonly, on one side, and (2) pain or tenderness on pressure upwards beneath the angle of the lower jaw. But if mumps is not suspected thus early, the first sign is likely to be slight swelling of one or both parotids. Usually one gland is affected before the other, but both may enlarge simultaneously or the process may be confined to one gland throughout. The affected gland steadily and rapidly enlarges, filling up the recess between the mastoid process and the ascending ramus of the inferior maxilla, until its anatomical outline, including the portion overlying the masseter muscle, is obvious. The skin overlying the gland becomes stretched and shiny, and sometimes slightly flushed rather than reddened. The appearance of the patient with bilateral parotitis is unmistakable. As the gland swells, and temporarily ceases to function adequately, the secretion of saliva is diminished and the mouth becomes dry, the tongue furred and the breath foul. Two transient mechanical effects may attend great enlargement, viz., trismus and deafness. (It is to be noted, however, that true nerve deafness of nuclear origin may complicate an attack of mumps.)

The temperature remains raised until the affected glands begin to subside, which happens in a few days. There may be marked bradycardia during the period of maximum enlargement. Constipation is the rule. With the subsidence of the parotid swellings the attack may be at an end, but it is not uncommon for one or both submaxillary salivary glands to be involved, either simultaneously with the parotids or later; less commonly the sublingual salivary glands are affected as well. An attack of "mumps" may involve all the salivary glands, or only one, or one pair.

Complications.—(i) *Orchitis*, which is usually unilateral occurs most commonly at puberty and during early manhood.

Stengel (1936) finds that only five cases of orchitis have been reported before the twelfth year of age. Although exceptionally orchitis appears to precede the parotitis, and according to some to occur "spontaneously" without parotitis, the condition almost invariably occurs after the parotitis and pyrexia have subsided. There is a sharp return of pyrexia which may attain 105° F., the pulse rate being correspondingly increased. The patient feels anxious and ill. On examination, tenderness, swelling and possibly fluctuation of one testicle are found. Coincident with the increased swelling of the testicle, which may attain a large size and be hard and tense to palpation, the patient experiences considerable pain. The attack of orchitis lasts for ten days; thereafter the swelling subsides and the temperature falls by lysis, rarely by crisis. At the height of the attack, delirium, stupor or mania have been noted, and Stengel says that meningitis or encephalomyelitis (of the aseptic type) may often be present.

The sequel to orchitis may be diminished sexual power: the real incidence of sterility is debated. *Feminism* has followed bilateral orchitis. (ii) *Mastitis* and (iii) *oöphoritis* are of much rarer occurrence than orchitis.

(iv) *Pancreatitis.*—Mumps-pancreatitis is an uncommon but important complication. Bradbury and Scheffer (1931), in an analysis of 252 cases of mumps, found thirteen cases of pancreatitis. It has been stated (Feiling) that mumps is the commonest cause of pancreatitis in children. It occurs in boys more often than girls (Farnham, 1922), and usually follows the parotitis, but may precede it. Mumps-pancreatitis without parotitis has been recorded. The *onset* is acute with epigastric or left hypochondrial pain, nausea and vomiting. The temperature is moderately raised; the pulse is not correspondingly increased; it may be slow. Constipation or diarrhœa may occur. The stools contain fat droplets, the urine, acetone and diacetic acid and, exceptionally, sugar. There may be an increase in the blood sugar. Palpation of the epigastrium occasionally reveals a sausage-shaped tumour. Spontaneous recovery is the rule. In an analysis of 119 cases Farnham (1922) found only one fatal example.

(v) *Diabetes* rarely follows mumps, but mumps occurring in a diabetic may have serious results. Patrick (1924) observes that although occurring in mumps-pancreatitis, abdominal pain is *absent* in mumps-diabetes.

(vi) *Nervous Complications.*—These occur chiefly in adults.

(*a*) *Encephalitis or meningo-encephalitis* may be one of the prodromal manifestations, or may occur after the acute stage:

recovery usually follows without residual damage (*vide* Chapter XXIII).

(*b*) *Meningitis.*—" Cerebral mumps " with symptoms of meningeal involvement at the onset was not very uncommon during the Great War. In many cases the condition was meningism, but true meningitis—the cerebrospinal fluid being clear, under greatly increased pressure, with marked lymphocytosis—may occur nearly always combined with orchitis (*vide* Chapter XXIII).

(*c*) *Cranial Nerves.*—One or several of the cranial nerves may be involved, particularly the optic, facial and auditory, sometimes in sequence. Usually the resulting paralyses are temporary, but permanent *nerve-deafness* may follow an attack of mumps. *Optic atrophy* may also result.

(*d*) Temporary *polyneuritis* is an uncommon happening.

(vii) *Œdema of the glottis* is an alarming event which has occurred during attacks of submaxillary mumps. Harries and Benn (1930) reported two cases of œdema of the tongue in association with solitary sublingual mumps.

Diagnosis.—The diagnosis of bilateral parotid mumps presents no great difficulty : unilateral parotitis and solitary submaxillary or sublingual mumps present greater difficulties unless a history of exposure is obtainable. It is important definitely to ascertain by careful examination that the parotid gland is in fact involved, and always, of course, to inspect the fauces. The result of casual examination may be tragic if the **bull-neck of toxic diphtheria** is mistaken for mumps (*vide* Chapter XIII).

The following causes of enlargement of the parotid gland must be excluded :—

(i) *Suppurative parotitis* (unilateral or bilateral) may occur in conditions in which the mouth tends to become foul, *e.g.*, enteric fever, coma due to uræmia or cerebral abscess, post-operative parotitis.
(ii) *Salivary calculus* (unilateral).
(iii) *Tumours* (unilateral).
(iv) *Drugs*, *e.g.*, mercury and iodides (bilateral).
(v) *Heat stroke* (bilateral).
(vi) *Miculicz's syndrome* : symmetrical, chronic, painless enlargement of all the salivary glands *and* the lachrymal glands.
(vii) *Heerfordt's Syndrome* (uveo-parotid tuberculosis).—Chronic disease of the uveal tract and parotitis, and possibly signs of a tuberculous focus.

Prophylaxis.—*Infectivity.*—Mumps is conveyed by droplet spray, the infective agent being present in the saliva and nasal secretions certainly during the early stages of the disease, and probably longer. Infectivity possibly persists, as is commonly believed, until the affected glands have returned to their normal size. Mumps is not highly infectious, close personal contact, or the use of handkerchiefs, spoons, etc., which have been contaminated, is necessary for spread. An important source of infection is the missed abortive or atypical case, such as solitary sublingual mumps.

Isolation must be maintained until the swelling of the gland last affected has completely subsided. Provided that all swelling has been absent for a week, the patient may be released from isolation two weeks after the commencement of the attack.

Quarantine.—In institutions it may be desirable to place exposed susceptible children in quarantine, and this must be imposed for thirty days. At least during the latter half of this period temperatures should be taken morning and evening. Evidence of pyrexia or malaise should lead to an examination for the presence of papillitis of the orifice of Stensen's duct.

Disinfection.—All crockery and utensils used by the patient must be boiled immediately after use : swabs and handkerchiefs should be burnt or boiled. Ordinary " spring-cleaning " of the room suffices after the release of the patient.

Seroprophylaxis.—The injection of human immune serum or whole blood has had a measure of success, and especially among older boys who are liable to orchitis may be worth trying. Hess employed *whole blood* obtained from children at various stages after an attack of mumps. One injection apparently protected susceptible children who were definitely exposed.

Regan (1925) injected an average dose of 2 c.c. of convalescent serum from the first to the sixth day after exposure. In a group of seventy children who were under observation until the end of the incubation period, one developed mumps. Regan obtained most of his serum from children fourteen to sixteen days after the attack.

Gunn (1930) found injection on the first day after exposure to be " highly satisfactory," but although on the whole the results were inconclusive they justified further trial.

Treatment.—The treatment of mumps is purely symptomatic. Rest in bed until the glands have subsided is especially important for boys at or over the age of puberty. Careful

attention to the bowels and to the hygiene of the mouth is essential. Difficulty in opening the mouth for feeding may necessitate the patient taking fluids through a straw. Chewing-gum promotes the flow of saliva and helps to keep the mouth clean. The occurrence of orchitis necessitates a suspensory bandage and some soothing application such as a glycerin of belladonna. The pain of orchitis may require morphia for its alleviation.

SUMMARY OF CHAPTER XIX

Mumps is caused by a virus ; any or all of the salivary glands may become swollen. The swellings subside without suppuration.

Complications (*metastatic*): Orchitis, mastitis, oöphoritis, pancreatitis. Nervous complications. Œdema of the glottis.

Diagnosis from other swellings of the parotid gland, and from the " bull-neck " of toxic diphtheria.

CHAPTER XX

GLANDULAR FEVER

(Infective Mononucleosis)

DEFINITION.—Glandular fever in its typical form is characterised by a prodromal stage of malaise and pyrexia, sometimes accompanied by sore throat and followed, after a variable interval of days, by enlargement of the cervical lymphatic glands and in many cases by splenomegaly. Absolute lymphocytosis with monocytosis occurs. The red cells are unaltered in the acute phase. Infectivity is slight. Children and young adults are chiefly affected.

Ætiology.—Filatow (1885) noted what he believed to be the idiopathic enlargement of lymphatic glands in children, and Pfeiffer (1889) described the clinical characteristics of the disease which he named *Drüsenfieber*. Many years elapsed before it was realised that associated with the adenopathy were characteristic changes in the blood picture. Cases of adenitis with mononucleosis were recorded by Türck (1907) and others, and were believed to be isolated examples of pseudo-leukæmia or "acute leukæmia with recovery." Then Sprunt and Evans (1920) described "infective mononucleosis" and shortly afterwards Tidy and his co-workers (1921), as the result of their investigations of an epidemic in London, were able to integrate the earlier clinical and hæmatological observations and to show that infective mononucleosis was identical with glandular fever (Pfeiffer), and this in turn with pseudo-leukæmia.

Since then, in addition to the Pfeiffer type of the disease, an anginose form (monocytic angina) and a febrile type (Tidy, 1934) have been differentiated. It has been objected by some that these are not all the same disease, but the more general opinion is that one type may merge into another and that a single case may share the characteristics of all three types.

Glanzmann has recently endeavoured to elucidate the systematic relationship of glandular fever and similar benign infective processes (benign lymphoblastoses) with the true leukæmias (malignant lymphoblastoses). In this connection the observations of Mervyn

Gordon (1936) on lymphadenoma may be mentioned. Gordon believes that the infective agent of Hodgkin's disease is morphologically similar to the Paschen bodies now recognised as the virus of vaccinia. Others regard lymphadenoma as allied to the leukæmias and as in the nature of a neoplastic reticulosis. Davidson (1937), Sprunt and Evans (1920) and Longcope (1922) showed that the histological appearances of the glands in glandular fever were very similar to those of lymphadenoma.

Pratt (1931) described the *histological features* of the excised glands in glandular fever as follows : "There were numerous hæmorrhages . . . several small arteries showed intravascular clotting. Most marked was the very considerable hyperplasia of the reticulo-endothelial cells . . . indicating a toxæmia, possibly due to infection with a filterable virus."

Although the disease occasionally attains *localised epidemic* prevalence, *sporadic* cases are of more frequent occurrence. Some of these undoubtedly escape detection and maintain the chain of infection. Although in this country at least two epidemics (in 1920 and 1930) have been recognised, the disease would appear to be more prevalent, or at least more frequently recorded, on the Continent and in America.

Most cases occur in spring and autumn. Glandular fever affects infants and older children, although numerous examples in adolescents have been recorded. The maximum incidence occurs at the age of five, boys being attacked more frequently than girls. Recoveries in glandular fever are the rule : deaths are due to concurrent conditions.

Incubation Period.—This ranges from five to fourteen days ; exceptionally, twenty-one days.

Clinical Features.—(*a*) GLANDULAR TYPE (Pfeiffer's Type).—This is the characteristic form of the disease, although, owing to the variable features of the prodromal illness and to the fact that different groups of glands are affected, or affected in differing order in individual cases, the clinical picture may be far from clear-cut. The common order of events is as follows : there is a sharp febrile onset, the temperature ranging from 101° to 102° F., exceptionally to 104° F. There may be nausea or vomiting. Thereafter ensues a period of malaise lasting from one to five days, associated with headache and pains in the limbs. In some outbreaks, especially among young adults, an initial tonsillitis, usually without exudate, has occurred. Epistaxis is an occasional feature, as also is abdominal pain or tenderness. Following the prodromal period the lymphatic glands commence rapidly to enlarge, and may attain the size of a plum or small egg.

Glanzmann has recognised the following forms of the glandular type :—

(i) *Cervical Form.*—Typically, the glands of the *cervical groups* are most constantly and most markedly affected, especially those underlying the sterno-mastoid muscle. For some reason, *left-sided* cervical adenopathy frequently occurs first. Palpation elicits tenderness and tenseness. Elasticity similar to that of the glands in lymphadenoma is also to be noted. Although ordinarily those earliest and chiefly involved, enlargement is not confined to the cervical groups. Later, and to a lesser degree, the sub-occipital, submaxillary, axillary and inguinal groups may be affected. Enlargement of a solitary gland in these situations may occur.

Opinion is divided as to whether the *parotid* glands ever become enlarged. Tidy believes not, the lymphatics overlying the parotid alone being affected.

(ii) *Mesenteric Form.*—On the other hand, glands of the external groups may not be at first affected, or, indeed, affected at all. There may be primary enlargement of the *mesenteric glands*, a fact of great importance, since, in such cases, the conjunction of vomiting, pyrexia, abdominal pain and tenderness is suggestive of appendicitis.

(iii) *Tracheo-bronchial Form.*—Again, enlargement of the *tracheo-bronchial group* may give rise to the clinical picture of a respiratory tract infection, a harsh cough, catarrh and possibly bronchitis being the outstanding features.

(*b*) ANGINOSE TYPE (*Monocytic Angina*).—In this type the prodromal stage is usually prolonged, and is followed by the formation of pseudo-membrane upon the fauces.

Splenomegaly.—In about half the cases of glandular fever of Pfeiffer's or the anginose type, the spleen is enlarged to palpation usually a few days after the initial enlargement of the lymphatic glands.

(*c*) FEBRILE TYPE.—The main features are as follows :—

(i) An abrupt onset with sore throat, the fauces being reddened.

(ii) Prolonged pyrexia which may exceed a month ; the temperature, at first remittent, may later become intermittent.

(iii) Considerable constitutional disturbance.
(iv) The late occurrence of glandular enlargement (third week of illness).
(v) Splenomegaly is unusual.
(vi) The appearance during the first week of the illness of a *rash*. The *distribution* of the rash is chiefly on the trunk; sometimes it occurs sparsely on the face. The lesions are macules or papules, pink or pink with a tinge of brown, and may appear in crops. The papular or maculo-papular rash resembles that of *paratyphoid fever*; *exanthematic typhus* has also been suspected. The macular rash may resemble either measles or rubella.

Blood Picture.—The essential blood picture is an increase in white cells with a high percentage of *monocytes*. These typically show a large bilobed nucleus which stains faintly. There may, however, be a *transient polynucleosis* in the prodromal and initial stages according to Poole and Findlay (1936). These observers state that leucocytosis and glandular enlargement usually occur together, the leucocytes ranging from 6,000 to 15,000 per c.mm.; but the high counts which are common in lymphoid leukæmia do not occur in glandular fever. Monocytes constitute 60 to 70 per cent. of the white cells. Numerous types of abnormal monocytes are usually present simultaneously, which is in marked contrast with lymphoid leukæmia. "It is further to be noted that the blood changes are not unlike those of whooping-cough, mumps, rubella and agranulocytosis" (Poole and Findlay, 1936).

There is no change in the numbers, appearance or hæmoglobin content of the *red cells* in the acute phase of the disease; slight anæmia may be associated with the debility of convalescence.

Depending to an extent upon the type of the disease, pyrexia persists for few or many days. The glandular enlargement gradually subsides, without suppuration, unless secondary infection has occurred; but complete regression to normal of the glands or spleen may not take place for many months.

Complications.—Especially in the *febrile type*, *hæmaturia* may occur, but this complication, although relatively frequent in some outbreaks, is uncommon in others. In association with the same type, muscular pains in the neck may lead to suspicion of *meningitis*.

Combined Infections.—Glandular fever may be combined with diphtheria or scarlet fever.

Diagnosis.—The diagnosis of a sporadic case of glandular fever may present considerable difficulty and on clinical evidence alone be impossible. Differential blood counts are essential, but may need the additional support of serological tests.

The *clinical* pitfalls vary with the type of the disease.

(*a*) *Glandular Type.*—The acute leukæmias, myeloid, lymphoid and monocytic, must be excluded. In the later stages of acute lymphoid leukæmia there is a swinging temperature, the lymphocyte count is higher than any encountered in glandular fever and there is anæmia. The recently differentiated monocytic leukæmia (Osgood, 1937; Smith, G. S., 1937) may present considerable difficulties, not only because of the monocytosis but because the enlargement of the lymphatics and the spleen is less constant and less marked than in the other leukæmias. The illness, however, is acute and is characterised by swelling of the gums, stomatitis, purpura and hæmorrhages, weakness and fever, as distinct from the comparatively slight departure from health which attends glandular fever.

In *lymphadenoma* the affected glands, although hard and elastic as in glandular fever, are not tender. The blood picture in Hodgkin's disease shows no increase in lymphocytes.

(*b*) *Anginose Type.*—Cases of acute lymphoid leukæmia not uncommonly present, at some stage, pseudo-membrane on the fauces, which is mistaken for *diphtheria.* The latter disease must also be differentiated from glandular fever: the false membrane, which may be extensive, and the considerable enlargement of the cervical glands coexist in glandular fever with comparative well-being of the patient, who, were the condition diphtheria, would be gravely ill. A bacteriological report, negative for the diphtheria bacillus, and the blood count should serve to exclude diphtheria. *Vincent's angina* may occur in association with the anginose type (*vide* Chapter XIV). *Agranulocytic angina* must also be borne in mind: the patient, usually but by no means always an adult of middle age, is gravely ill; there may be a history of drug administration, *e.g.*, amidopyrine; the white count shows that *granulocytes* are diminished or absent.

Especially as the Wassermann reaction is moderately positive in about half the cases of glandular fever, *secondary syphilis* must be excluded: the symmetrical snail-track ulcers, the symmetrical polyadenitis, anæmia, alopecia, possibly a roseolar rash (which, however, avoids the face) and sometimes

evidence of a primary sore, together with strongly positive Wassermann reaction, should prevent this unfortunate mistake.

(c) *Febrile Type.*—The maculo-papular eruption, appearing after some days of pyrexia, may be confused with that of enteric fever or with exanthematic typhus (the typhus rash *avoids* the face). A negative Widal test should exclude the former and a negative Weil-Felix (*typhus*) reaction the latter. Measles is differentiated by the absence of Koplik's spots (but *conjunctivitis* may occur), and by the fact that the morbilliform rash of glandular fever either avoids or occurs sparsely on the face.

Rubella may be more difficult to exclude; but the long prodromal period and the considerable prostration in this type of glandular fever, and the late occurrence of glandular enlargement which is both visible and palpable, are quite unlike that of rubella, although the blood picture may be very similar.

Serological Diagnosis.—Paul and Bunnell (1932) devised a test which is based upon the presence of sheep heterophile antibodies in the blood of the patient suffering from glandular fever, and is, according to Stuart and Mickle (1936), almost specific. Serial dilutions of the patient's serum are made, and to them are added a suspension of washed sheep's corpuscles. The tubes are incubated at 37° C. for from two to four hours and the degree of agglutination noted. "With confirmatory clinical and cytological evidence, a titre of 1 in 80 to 1 in 10,000 gives, with few exceptions, a positive diagnosis. The chief exception is the blood of patients who have been injected with horse serum, since their blood may develop sheep heterophile antibodies, which, however, are completely absorbed by emulsions of guinea-pig kidney, while those of glandular fever are not" (Stuart and Mickle).

Prophylaxis.—The infectivity of glandular fever is slight: spread of infection may be presumed to be by droplet-spray under conditions of close contact and possibly by articles soiled with saliva. The patient should be isolated for a fortnight, and, if imposed, quarantine of contacts should last for the same period.

Treatment.—The treatment of glandular fever is purely symptomatic. Considerable debility may follow an attack; convalescence must not be hurried.

SUMMARY OF CHAPTER XX

Types: Glandular, anginose, febrile.
Manifestations: Adenitis, splenomegaly, monocytosis.

CHAPTER XXI

CHICKENPOX

(Varicella)

DEFINITION.—Chickenpox is a mild highly infective disease caused by a filterable virus. After a variable incubation period, commonly a fortnight, and trifling prodromata, crops of papules appear which attain a centripetal distribution. The lesions of each successive crop pass through the stages of vesiculation and pustulation. The result of cropping and relatively rapid evolution is that lesions in various stages are usually evident upon the skin at the same time.

Ætiology.—*Incidence.*—Chickenpox is cosmopolitan. Endemic in all large centres of population, it attains epidemic prevalence at irregular intervals. Outbreaks in children's institutions and hospitals are common.

Seasonal Prevalence.—Chickenpox tends to be more prevalent in autumn and winter. P. Stocks (1930) showed that in one of the London boroughs "in each of the seven years (1923-29) there was a peak either in June or July, and, except in the last year, a second peak in October or November." The summer peak was small and this was followed by a considerable peak in the autumn.

Age Incidence.—Children under ten years of age are chiefly affected. Infants under a year appear to possess a temporary immunity, probably maternally transmitted. They are rarely attacked, but when an attack does occur the eruption tends to be profuse. S. D. Collins (1929) estimated that in the United States more than 50 per cent. of children contract the disease by the age of seventeen years. Since in the adult attack is relatively rare, there may be a process of latent immunisation as in other of the acute specific infections. *Sex incidence* is equal.

Mortality.—Deaths ascribed to chickenpox are nearly always due to some intercurrent or superimposed infection (*vide infra, Varicella gangrenosa*).

Causal Agent.—Chickenpox is caused by a filterable virus. C. R. Amies (1933) demonstrated in the vesicle-fluid elementary

bodies very similar to the Paschen bodies of smallpox. These elementary coccus-like bodies are specifically agglutinated by the serum of chickenpox convalescents, and Amies considers that their constant presence in the lesions and their agglutinability by homologous antiserum is strong evidence that these elementary bodies are the actual infecting agents.

Mode of Spread.—Chickenpox is primarily an infection of the upper respiratory tract. The *infectivity* of the disease in its early stages is very great. The virus is ordinarily conveyed by droplet spray, or by air currents, *e.g.*, draughts of air through open hopper-windows in "cubicles" or chambers. Some maintain that the virus may be disseminated by aerial convection over distances of many feet, but the probability of its conveyance upon the hands, hair or clothing of the attendants and upon utensils is much greater and undoubtedly accounts for many instances of cross-infection in wards. Infectivity is greatest in the earliest stages; possibly towards the end of incubation. F. Thomson considered that infectivity rapidly declined, and that by about the third day of the eruptive stage had ceased. However, as in smallpox it is customary to regard the crusts of the dried lesions as potentially infective, and recent work, already mentioned, rather supports this view.

The relationship of chickenpox to herpes zoster is discussed later, but here it may be mentioned that the appearance of a case of herpes zoster in a children's ward is not uncommonly followed by an outbreak of chickenpox.

Incubation Period.—The incubation period is variable; **fourteen** to **fifteen** days may be regarded as most usual, but periods shorter than two or longer than three weeks have occurred. Following the occurrence of herpes zoster the incubation period is usually fourteen days, although von Bokay has recorded periods of from seven to twenty-four days as elapsing before the resulting chickenpox cases appeared.

As in other acute specific infective diseases, exceptionally short or long periods should always give rise to suspicion of a missed case.

Clinical Features.—(*a*) *Prodromata.*—The occurrence of recognisable prodromal symptoms is by no means constant, especially in young children. The first clinical event may be the appearance of the eruption. In older children and adults, however, prodromata consisting in headache, pains in the limbs, nausea or vomiting and pyrexia (101° to 102° F.) may occur, and for a period of twenty-four hours the patient may feel quite ill. As in smallpox, sore throat sometimes occurs but, as in that disease, is part of the enanthem and is attributable

to the appearance of the lesions on the fauces and palate. (The *duration* of the prodromal illness is important in connection with the differential diagnosis of smallpox (*q.v.*).)

Prodromal Rashes.—With or without general symptoms of initial toxæmia, a prodromal rash may precede the focal eruption. The commonest type of rash is scarlatiniform and is frequently mistaken for the rash of scarlet fever. Rarely, a morbilliform prodromal rash occurs.

The scarlatiniform rash may be clinically identical, both in distribution and character, with the rash of scarlet fever, although confirmatory tests for scarlet fever (*vide* p. 109) are negative. At other times the rash is a dull red erythema, not punctate, appearing first and most uniformly upon the back, which may be wholly invaded; next, and more sparsely, perhaps in patches the size of the palm, upon the chest and abdomen and sometimes upon the adductor surfaces of the thighs. Close inspection may reveal, first upon the back, the presence of papules set upon the erythematous field. In a few hours, as the papules appear so the erythema fades, leaving wide irregular zones around each lesion. These, too, soon disappear, the focal lesions alone remaining.

Nevertheless, the possibility of concomitant chickenpox and scarlet fever must be borne in mind.

(*b*) *Eruption.—Character of the Lesions.*—In the earliest stages the lesion of chickenpox is a macule or maculo-papule which in a few hours becomes definitely papular; the colour varies from dark pink to dark red. A few hours later still the *papule* becomes changed into a clear *vesicle* which has the following characteristics: (i) it is *superficial*, being situated "on" rather than "in" the skin. There may or may not be an areola, but if not, the vesicles have a general resemblance to drops of water or glass-beads, hence the old popular name "glass-pox." If there is any doubt as to the superficiality of the lesions, one of them should be rolled gently between finger and thumb. (ii) the vesicles tend to have shallow walls and many of them are *elliptical* in plan. The elliptical lesions should always be sought if there is any doubt about the diagnosis. They are highly characteristic, and some are usually to be found on the lower quadrants of the abdomen and on the lumbar region. Invariably the major axis of the ellipse runs *parallel* with the natural folds of the skin—*never* across. (iii) the vesicle is *unilocular*: pierced with a needle the walls collapse (*cf.* smallpox). So fragile are the walls that they are readily ruptured by a touch with the finger-nail or by the pressure or chafing of the garments. Occasionally dimpling

of the apex is seen (*cf.* umbilication in smallpox). Few or many papules or vesicles may abort and dry up.

Skin organisms in the course of a few hours invade the vesicles, the contents of which become first turbid and then

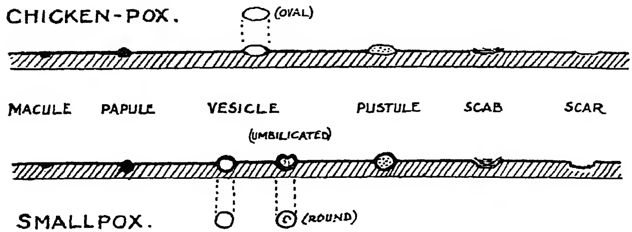


FIG. 25.—Diagrammatic Representation of the Differences between the Focal Lesions of Chickenpox and Smallpox.

purulent. These *vesico-pustules* are usually surrounded by an inflammatory zone. In the course of twenty-four hours or so the pustules commence to shrivel; the edges are *crenated.* Fine *striæ*, the result of shrinkage, may be observed on the flattened root of the lesion—the striæ running parallel with the long axis of elliptical lesions.

During the course of the ensuing two to four days the pustule dries up to form a scab. The scab after a variable interval separates, leaving a shallow cicatrix which is at first pink but later becomes dead-white. It is important to become familiar with the appearance and distribution of the scars as they are the only evidence of a previous attack.

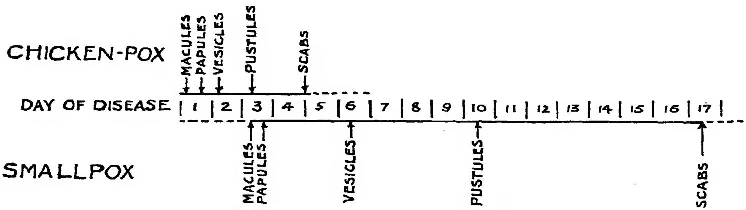


FIG. 26.—Diagram comparing the Evolution of the Focal Lesions of Chickenpox and Smallpox. Note the more leisurely development of the rash of smallpox.

The relatively rapid evolution of the individual lesions of chickenpox from papule to pustule is in contrast with the slower progress to maturation which occurs in smallpox

Order of Appearance of the Papules: Distribution.—1. *Enanthem.*—The earliest lesions of chickenpox appear upon the buccal and pharyngeal mucosa, although they are not always visible to the naked eye. The buccal cavity should always be inspected for lesions. It is not uncommon to find them, already pustular, upon the hard or soft palate in conjunction with later papular or vesicular lesions on the skin. It is to be noted that although lesions may occur in the mouth in either chickenpox or smallpox, they do *not* occur in this situation in two conditions which frequently have to be differentiated, viz., urticaria papulosa and scabies.

2. *Exanthem.*—The cutaneous lesions appear in crops, the papules commonly appearing earliest and most profusely upon the back: hence in the fully developed eruption the most mature lesions, and the most thickly set at any stage, are to be seen in this region. The chest and abdomen are next invaded and ultimately may attain a density, especially upon the lower abdomen, nearly as great as upon the back. Usually the face is next invaded and finally the limbs. The *order of appearance* is also, generally speaking, the *order of density*. As further crops appear the relative density of distribution is maintained. Inspection of the skin picture when the eruption is fully developed shows the following characteristics (*vide* Fig. 27):—

(i) *Centripetal Distribution.*—Most lesions on the trunk, especially upon the back; more lesions upon the upper arms and thighs than upon the forearms and legs; more lesions below an imaginary line drawn through the nares and the lobes of the ears than above this line. It is to be noted that in chickenpox, as in smallpox, lesions may appear upon the dorsum of the hand and foot and upon the palm and sole, but the distribution of the eruption of smallpox being centrifugal, the relative density upon the (proximal) upper arms and thighs and the (distal) forearms and legs is reversed. Although the centripetal pattern is maintained, the ultimate profusion of the lesions varies greatly. In some cases three to five successive crops may occur and the lesions become so densely set as to be semiconfluent upon the trunk; in others only a single crop or even a single lesion may appear.

(ii) *Concavities and Flexures.*—Ricketts pointed out that the lesions of chickenpox tend to occur in relatively greater abundance in concavities and protected parts than upon convexities and exposed surfaces as is the case in smallpox. Thus in chickenpox lesions will be found, sometimes in abundance, in the axilla and within the cavity of the orbit.

(iii) *Lesions in all Stages of Development.*—Papules, vesicles, pustules, and possibly scabs, are to be seen at the same time.

Unusual Sites.—Occasionally lesions appear upon the palpebral or ocular conjunctiva. In the former situation they give rise to no trouble, and lesions upon the ocular conjunctiva nearly always remain quite superficial and heal without residual opacities; a very few cases of *keratitis* have, however, been reported. *Intralaryngeal* and *intratracheal* lesions are rare. Lesions within the larynx have still more rarely given rise to such a degree of obstruction as to necessitate tracheotomy. Lesions upon the *vulva* and within the *prepuce* have also been recorded.

Clinical Course.—The clinical course of an attack of chickenpox is usually uneventful. If prodromal symptoms occur they are accompanied by slight or moderate pyrexia—rarely exceeding 102° F., and by a proportionate increase in the pulse rate. In cases without obvious prodromata there may nevertheless occur slight increase in the temperature and pulse rate before the appearance of the eruption, and slight rises in temperature may be noted just before the appearance of successive crops. Unless the lesions which attain the stage of pustulation are very numerous or become the foci of severe pyococcal infection, "maturation" gives rise to no anxiety. Many attacks of chickenpox are afebrile throughout. *Second attacks* are uncommon, but undoubted.

Unusual Forms.—(i) *Varicella Hæmorrhagica.*—This type is very rare and very fatal. Hæmorrhages occur not only into the vesicles but into the skin (ecchymoses and petechiæ) and the subconjunctival spaces. In the most severe forms bleeding from the intestinal mucosa occurs, as shown by the vomitus and the presence in the stools of altered blood.

(ii) *Varicella Bullosa.*—In this type of chickenpox few or many of the lesions become bullous. Although the condition may occur independently of other obvious sources of pyococcal infection, *V. bullosa* is most likely to be encountered in children who have *impetigo*, or where there is concurrent measles and especially scarlet fever, *i.e.*, when there are abundant opportunities for infection of the lesions with hæmolytic streptococci. (When chickenpox and scarlet fever are concurrent, pustulation tends to be severe and to be followed by *ulceration.* If the process is extensive the child may die from septic absorption with terminal broncho-pneumonia.)

(iii) *Varicella gangrenosa* is divided by Banks and McCartney (1937) into (*a*) fulminating, and (*b*) subacute.

(*a*) *The fulminating type* is due to infection of the lesions

with a strain of the hæmolytic streptococcus. It is characterised by extensive necrosis of the lesions and intense toxæmia, which has usually proved fatal within a few hours. In the cases described by Banks and McCartney, including one of their own, massive skin gangrene in a single lesion accompanied by a few similar smaller lesions occurred early in the eruptive stage. Their patient had tonsillitis, and from the tonsils and the skin lesion a hæmolytic streptococcus of Type 23 (Griffith) was recovered.

(*b*) *The subacute* type has been shown in several recorded cases to be due to the infection of the lesions with virulent strains of the diphtheria bacillus. In some instances an obvious focus of infection, *e.g.*, anterior nasal diphtheria, has been present. In this type few or many of the lesions fail to heal in the ordinary way, but become the sites of black necrotic sloughs : if the slough be removed, a deep punched-out ulcer remains. Banks and McCartney point out that these necrotic lesions appear *late* in the attack of chickenpox. Their ætiology may only become manifest on the occurrence of one or other of the post-diphtheritic complications, *e.g.*, palsies, myocarditis or heart-block.

(iv) *Herpes Zoster.*—The virus of chickenpox is ordinarily *dermatotropic,* but may exhibit *neurotropism.* Invasion of the posterior root ganglia giving rise to an attack of *herpes zoster* may be the sole clinical manifestation of an attack of chickenpox. Occasionally, herpes zoster is combined with an ordinary attack of chickenpox. Such a conjunction probably corresponds with cases formerly referred to as "aberrant herpes." The earliest observers to draw attention to the connection between chickenpox and herpes zoster were von Bokay of Budapest and Le Feuvre of Buluwayo, who noted the occurrence of outbreaks of chickenpox following exposure to a case of herpes zoster, and much more rarely the opposite, *i.e.*, herpes zoster occurring in patient exposed to chickenpox. Many have held, and some still hold, the view that the sequences are purely fortuitous, but nearly all who work in children's wards have long been convinced of the connection, and we invariably isolate immediately a child who develops herpes zoster. Even so, this precaution is frequently without avail, and an outbreak of chickenpox occurs a fortnight later. It is not suggested that in every instance the causal agent of herpes zoster is the virus of chickenpox. It has been mooted, however, that in herpes zoster apparently caused by, for example, arsenic, the drug activates a latent virus infection.

Netter showed some years ago that cross-complement

fixation was obtainable by using as antigen the vesicle contents or dried scabs of chickenpox or zoster respectively. Much more recently Amies has shown that elementary bodies apparently identical with those present in chickenpox vesicles can be demonstrated in the vesicle-contents of herpes zoster. Histologically, the vesicles of chickenpox and herpes zoster are identical in appearance.

Nervous Complications.—That the neurotropic affinities of the virus of chickenpox are not confined to the posterior-root ganglia is shown by the rare occurrence at some stage in the attack of chickenpox of such conditions as meningo-encephalitis and encephalitis. E. Ashworth Underwood (1935), as the result of an exhaustive clinical and epidemiological study, concludes that varicella encephalitis "is essentially due to the development of neurotropism by the virus of varicella."

Underwood divides the recorded cases of nervous complications in varicella into the *nervous prodromata, convulsions* especially, sometimes followed by definite organic change, and into the following groups :—

Group 1. *Meningo-encephalitis* : typical features of meningitis at the onset ; later involvement of other parts of the nervous system may be present, but the meningeal signs still predominate. The cerebrospinal fluid is sterile.

Group 2. *Encephalitis*, comprising "exactly half of all the reported cases" of nervous complications, is by far the most important manifestation. Cerebellar forms, with a cerebellar syndrome consisting in ataxia, vomiting, speech changes, nystagmus, vertigo and tremor, are frequent and typical of varicella encephalitis. The occurrence of cerebellar types tends, Underwood remarks, to differentiate varicella encephalitis from post-vaccinal and other forms of post-infectious encephalitis. *Group* 3. Myelitis. *Group* 4. Neuritis and polyneuritis. *Group* 5. Ocular manifestations. *Group* 6. Other conditions.

The prognosis as regards recovery is good. There is no typical pathological picture : the findings are "probably different from those in post-vaccinal and post-infectious encephalo-myelopathies generally." Neither sex nor age affect the incidence. Although symptoms may develop either before or after the appearance of the eruption, Underwood states that in most cases the onset is *between the fourth and tenth day* after the appearance of the rash.

Diagnosis.—The diagnosis of a fully developed case of chickenpox is usually simple. Particular regard should be paid to the following points : (i) prodromal illness lacking or trifling ;

(ii) centripetal distribution of the eruption; (iii) relative profusion of lesions in concavities, *e.g.*, axilla and orbit; (iv) lesions present in all stages; (v) superficiality of lesions; (vi) occurrence of elliptical lesions.

Difficulties may arise when the lesions are early and/or sparse. A past history of chickenpox should never be accepted unless supported by typical scars: if no history is forthcoming, the scars, unless absolutely typical in appearance and distribution, should be regarded with reserve. The patient with doubtful lesions should be isolated on suspicion and examined again in a few hours: if the condition is chickenpox, vesicles may have developed from the first crop of papules and possibly additional papules may then be apparent. The conditions which have to be excluded are:—

1. *Smallpox.*—If the patient has been successfully vaccinated or re-vaccinated within five years (or even seven to ten years), smallpox can at once be excluded. But in the unvaccinated and in those who were vaccinated many years ago, smallpox is a possibility. The details of the diagnosis of smallpox are discussed in Chapter XXII. The main criteria may, however, be enumerated here: (i) prodromal illness of two to four days; (ii) *centrifugal* distribution of lesions; (iii) their relative profusion on *convex* and *exposed* surfaces; (iv) lesions present predominantly *in one stage or another*, *e.g.*, vesicles; (v) lesions deep set ("shotty"); (vi) circular in plan (*vide* Figs. 25, 27, and 28).

2. *Papular Urticaria* (Lichen Urticatus).—This is the condition most likely to give rise to difficulty. The lesions are haphazard in distribution, they occur without any definite arrangement upon the trunk; the ankles are frequently involved and lesions may appear upon the palms and soles. The face is rarely invaded; the mouth never. The lesions appear in crops chiefly at night and typically consist of erythematous patches, sometimes urticarial, each with a central papule occasionally surmounted by a tiny vesicle. The erythema fades leaving the papules. Itching is intense. Papular urticaria affects chiefly young children and tends to appear during some dietetic disturbance frequently associated with an excess of carbohydrate, *e.g.*, too many biscuits. Evidence of faded or pigmented lesions of a previous attack is frequently forthcoming.

3. *Scabies.*—Scabies, the vesicular lesions of which have become pustular as the result of secondary infection by scratching, is not uncommonly confused. Lesions never occur in the mouth. The face is not affected, except occasionally in children

in whom the distribution is frequently atypical. The diagnosis is made by finding the burrows between the fingers and toes, and, in children, on the palms and soles, and confirmed by the identification of the *sarcoptes scabei* removed from the burrows and examined under the microscope. *Impetiginisation* of the lesions may make the diagnosis more difficult.

4. *Insect Bites*—particularly gnat-bites on the face which have become septic must be borne in mind : note the central puncta.

5. *Urticaria.*—The irregularly shaped wheals of very varied size and haphazard changing distribution, together with a possible history of previous attack following the ingestion of particular foodstuffs, or, of course, prior injection of a therapeutic (horse) serum, should make diagnosis easy.

6. Among rarer skin conditions bearing at some stage more or less resemblance to chickenpox are various bullous eruptions, *e.g.*, bullous impetigo, streptococcal pemphigus, and the lesions of erythema multiforme, which are not infrequently diagnosed as either chickenpox or smallpox. Iodide and bromide rashes, the latter particularly, and *hydroa æstivale* may be mentioned.

Prophylaxis.—There is no reliable method of *specific prophylaxis*. Varicellisation, analogous to variolation (*q.v.*) has been attempted but, apart from its obvious objections, has proved unsuccessful. It should not be considered unless under exceptional familial conditions. Various workers have attempted to prevent an attack of chickenpox following exposure by the injection of convalescent serum. Blackfan, Peters and Conroy (1923), Welch (1924), Gordon and Meader (1929) and Gunn (1932) had varying measures of success. Schmidt (1924) failed. Amies (1933) has demonstrated specific agglutinins in the blood of convalescents, and instead of pooling serum from convalescents indiscriminately, believes that it may be possible by means of agglutination reactions to detect and select those sera which have a high antibody content.

Treatment.—The treatment of chickenpox is chiefly directed to the limitation of secondary infection of the lesions. If there are buccal lesions, especial attention must be paid to the hygiene of the mouth lest ulceration result. If lesions on the scalp are numerous, it is better to cut the hair short ; otherwise troublesome impetiginisation may occur. The head should be shampooed at frequent intervals and some mild mercurial or resorcin ointment applied.

In the ordinary cutaneous lesions, the early individual application of Mitman's paint (cresol 0·5, tannic acid 12·5, collodion flexile 100) undoubtedly limits the process of pustulation; many lesions dry up in the papular or vesicular stage. Treatment should be started as early as possible, preferably on the first appearance of each crop. The lesions should be cleaned with ether and two or three coats of paint applied in order to form a seal.

From recent personal experience it would appear that the oral administration of one of the sulphonamide drugs has a marked effect in aborting the pustular stage, and is certainly of great value in *varicella bullosa*.

The treatment of *varicella gangrenosa* requires special mention. As already stated the condition may be caused by the infection of the lesions with virulent hæmolytic streptococci (fulminating form) or diphtheria bacilli (subacute form). It is not desirable to wait for bacteriological confirmation before instituting treatment. *At the earliest possible moment every* case of varicella gangrenosa should be treated by (i) the injection of *both* scarlet fever and diphtheria antitoxins and (ii) the oral administration of a sulphonamide-group drug in full doses. Delay may result in a fatal issue in the fulminating type.

The *detachment* of the scabs is facilitated by the use of carbolised oil applied on a feather or small brush. No force must be used since the premature or vigorous separation of scabs results in the production of sores which detain the patient longer than if the scabs were allowed to separate naturally.

Isolation and Quarantine.—There is no fixed period of isolation. It is at present customary to detain patients until all the scabs have separated leaving firmly healed cicatrices. Special attention must be paid to the scalp.

Concurrent disinfection or destruction of all articles soiled by the patient, and the sterilisation by boiling of spoons and crockery is essential. The strictest aseptic nursing technique. *i.e.*, the wearing of gowns and scrubbing of hands. must be enforced upon the attendants.

Quarantine must be imposed upon contacts for a minimum of twenty-one days; a period of twenty-three days is safer, although if the occasion of contact is definitely known, the first ten days may be remitted or the conditions modified, *i.e.*, children in a ward should be kept in bed under daily observation from the tenth day of exposure onwards.

SUMMARY OF CHAPTER XXI

Causal Agent : Virus (similar to Paschen bodies in smallpox).
Clinical Features : Prodromal toxæmia lacking, or of short duration ; focal eruption (centripetal).
Diagnosis : From smallpox, skin diseases and drug rashes.
Prophylaxis : Specific ; convalescent serum (doubtful utility).
General : Quarantine or modified quarantine of contacts.
Treatment : Nursing and symptomatic.

CHAPTER XXII

SMALLPOX (*Variola*) AND VACCINIA

DEFINITION.—Smallpox is characterised by an initial stage of toxæmia, followed by a focal eruption which appears in a definite regional order and attains centrifugal distribution. The focal lesions, at first papular, become successively vesicular and pustular. Typically, pustulation is accompanied by a secondary illness due to septic absorption. The causal agent is a filterable virus identical with that of vaccinia (the Paschen bodies). Variant strains of the virus give rise to epidemic types of smallpox differing in clinical severity and infectivity. Against all these types vaccination confers immunity.

Incidence.—(i) *Geographical.*—Smallpox occurs all over the world either as an endemic disease with phases of epidemic prevalence or in epidemic form following its introduction into countries ordinarily free. The chief *endemic* centres, the reservoirs of infection from which smallpox may be disseminated, are :—

(*a*) India and Egypt, the sources of the severe or "classical" form of the disease known as *variola major*. In Europe, Russia, and in North America, Mexico, are important endemic foci of *variola major*.

(*b*) The West Indies, the United States of America and Canada are the chief foci of a type of smallpox predominantly mild and variously termed alastrim or (in this country) *variola minor*. This mild type of the disease was introduced into eastern England in 1922 and for a number of years spread, in smouldering fashion, to various parts of the country.

(*c*) In South Africa a similar mild form known as *amaas* or Kaffir-pox occurs.

(ii) *Climatic and Seasonal.*—Although the incidence of smallpox is independent of *climate*, prevalence does vary with season. In countries of temperate climate, the disease tends to be more prevalent in the cold winter months. In the tropics, prevalence is greatest during the hot season. In India,

L. Rogers (1926) has shown that prevalence varies with the absolute humidity of the atmosphere. When absolute humidity is low, prevalence increases ; before the breaking of the monsoon prevalence is great, but when the rains commence it declines.

(iii) *Age.*—Smallpox occurs at any age; from infants who may be infected *in utero* to old people. But since the disease is preventable by vaccination and re-vaccination (*vide infra*) age incidence is governed by the vaccinal state of the community. Among well-vaccinated populations smallpox, after introduction, does not spread. In the eighteenth century, before vaccination, nine-tenths of the deaths from smallpox occurred among children under five years of age and the remainder among those between five and ten years old (Creighton). A very high relative mortality among children obtained until the pandemic of 1837-40. This pandemic caused some 41,000 deaths at all ages in England and Wales alone. In the last year of the pandemic the first Vaccination Act was passed ; this provided for free vaccination which in 1853 was made compulsory.

In 1871-72 the last pandemic of smallpox occurred and caused 42,000 deaths in this country, more than during the four-year pandemic of a generation earlier, although, it must be added, the population had increased by a third to a half (Creighton).

> Creighton (" History of Epidemics in Britain ") says that the 1871-72 epidemic " brought out clearly for the first time the changes in incidence which had been taking place slowly since the pandemic thirty years earlier ; there was a shift in geographical incidence from country to towns and industrial areas the result . . . of the Industrial Revolution, and a shift in age incidence ; young persons and adults were affected more than infants and children."

Creighton was an opponent of vaccination and thus failed to ascribe the decreased incidence among children to the extension of that practice. In the 1902 epidemic of *v. major* London was severely affected and J. P. Marsden (1936) records that most of the patients removed to hospital were aged from twenty to twenty-five years. In 1898 the practice of vaccination commenced to decline with the provision for " conscientious objection." In 1922 *v. minor* invaded this country and spread widely during a number of years. Owing to its mild, or relatively mild, character the public came to regard the disease without apprehension and the decline in vaccination continued steeply until, at the present time, 40 per cent. or less of infants are so protected. The occasional sequel of post-vaccinal

encephalitis (*vide infra*) was also a factor which weighed heavily against vaccination for protection against a type of smallpox with trifling mortality. The unvaccinated state of the community is reflected in the fact that of 3,070 patients treated for *v. minor* in the hospitals of the Metropolitan Asylums Board the majority were aged between five and ten years (Marsden). Thus the wheel has come nearly full-circle and the age incidence of smallpox now approaches that of pre-vaccination days.

(iv) *Sex.*—At nearly all ages, males are attacked in greater numbers than females.

(v) *Case-fatality.*—In this country, the alternation of mild with severe epidemic types is no new phenomenon, and there is also evidence of the gradual decline in fatality of *v. major* before this type was replaced by *v. minor*. Thus in 1871 the case-fatality rate of patients treated in the London smallpox hospitals was nearly 45 per cent., but in the 1902 epidemic only about 17 per cent. Marsden reports that the case-fatality rate among 13,686 patients admitted to hospital with *v. minor* in the period 1928-34 was one-quarter of 1 per cent., and he adds that in nearly half the fatal cases smallpox was "merely a remote contributory factor."

Causal Agent.—Smallpox is caused by a filterable virus which has been identified as the elementary bodies described by Paschen (1906). These are found in the vesicle fluid of the lesions of smallpox and vaccinia alike. Guarnieri's inclusion bodies (1892) are believed to be aggregates of the Paschen bodies. Pure suspensions of these bodies obtained by centrifuging and passage through Berkefeld V filters have been shown by Eagles and Ledingham (1932) to be highly infective and agglutinable by the serum of smallpox patients. Amies (1932) has shown that pure suspensions of Paschen bodies derived from cases of *v. major* and *v. minor* show cross-agglutination; the serum of patients suffering from *v. minor* will agglutinate the Paschen bodies derived from *v. major* and vice versa. In the mild strain of the virus causal of *v. minor* "the toxic properties for the human organism have become suppressed" (Ledingham).

Modes of Spread.—Smallpox is primarily an infection of the upper respiratory tract, and the main mode of spread is by droplet spray in the early stages of the attack—and possibly towards the end of the incubation period, although this is disputed by most observers. The occurrence of outbreaks in this country, traceable to infected bales of cotton imported from Egypt, is presumptive evidence that the disease may be transmitted by mediate means, and it is generally agreed that

scabs are potentially dangerous sources of infection for long periods. It was held at one time that by aerial convection the infective agent might be conveyed in effective doses through distances such as a quarter of a mile and that therefore, for this reason, the neighbourhood of a smallpox hospital was dangerous. There are still some who hold this view, but the evidence in many of the alleged instances does not withstand critical examination ; undetected human vectors are much more likely. Nevertheless, smallpox of the classical type (*v. major*) is generally regarded as the most infective of the exanthemata, and the possibility of aerial transmission for short distances (*cf.* chickenpox) is accepted. There is no reason to suppose that the strain causal of *v. minor* is *disseminated* any less readily than that associated with *v. major*, but the low virulence of the former strain produces the *effect* of lesser infectivity. The dissemination of the virus of *v. minor* requires closer or more prolonged contact or propinquity than that of *v. major* if transmission in *effective* dosage is to occur ; in other words, the virus of *v. minor* must be transmitted in larger or repeated dosage to produce a clinical attack in the non-immune and *a fortiori* in the partially immune.

Pathology.—As already stated (*vide supra*), smallpox is primarily an infection of the upper respiratory tract, and Paschen (1932) has shown that the elementary bodies are to be found in profusion in the lesions of the enanthem (*vide infra*). From this primary focus the infection spreads to the lower respiratory tract and in the lung a viral focus is formed. From this focus the virus at length invades the blood stream and thus the skin and the viscera (Paschen). Death in smallpox may occur during the initial toxæmia from acute toxic myocarditis or encephalomyelitis, *i.e.*, from the effects of the virus itself, or during the stage of pustulation as the result of bacterial invasion, usually streptococcal, of tissues already damaged by the virus. Broncho-pneumonia, or lobar pneumonia, fatty degeneration of the liver and kidneys, a softened and enlarged spleen, together with myocarditis are the commonest post-mortem findings. If death has occurred from encephalomyelitis its pathological and histological changes are identical with those of post-vaccinal encephalitis (*q.v.*).

Blood Picture.—During the prodromal toxæmic and the succeeding papular stage, *i.e.*, for the first four or five days of the illness, leucopenia occurs with an absolute and relative decrease in the polymorphonuclears. Leucopenia is followed by leucocytosis, which reaches its maximum during the latter part of the stage of pustulation and continues during the period

of scabbing. The white count, which during the toxæmic stage may be 5,000 per c.mm. or less, may rise to 40,000 or more during the stage of pustulation. The leucocytosis is the response to the bacterial invasion of the lesions during pustulation.

Incubation Period.—(i) *Variola major.*—To the commencement of the prodromal stage the usual incubation period is **twelve** days ; or, to the first appearance of the rash, **fourteen** days. Ricketts gave the range of incubation to the outcrop of the rash as between eleven and seventeen days and considered that periods outside these limits should be looked upon with suspicion. Since, in mild cases, the symptoms of onset are apt to be vague, Ricketts preferred to reckon incubation to the *appearance of the rash* because this period is more constant and, especially in investigating outbreaks, this is the safer plan, particularly in the case of *v. minor*.

(ii) *Variola minor.*—The incubation period, reckoned to the appearance of the rash, tends to exceed fourteen days in a higher proportion of cases than in *v. major* ; periods of fifteen to seventeen days to the outcrop have occurred not uncommonly.

Clinical Features.—The clinical stages of an attack of smallpox are (i) the prodromal, pre-eruptive toxæmia followed by (ii) the appearance and evolution of the focal eruption which passes successively through papular, vesicular and pustular stages.

An attack of smallpox may be " natural " or " modified." By " modified " smallpox is generally understood an attack of *v. major* modified in its severity by the partial immunity of the host, but Marsden shows that attacks of *v. minor* are clinically identical with modified *v. major*, in this case modification being brought about by the degraded strain of the virus. Unmodified smallpox (*v. major*) will first be described and then the disease as modified by either of these factors.

(*a*) *Prodromata.*—The onset of the toxæmia of smallpox is usually, but not invariably, abrupt. Headache, backache, vomiting and pyrexia form a common syndrome of which the most constant elements are headache, usually frontal and accompanied by giddiness, and pyrexia (103° or 104° F.) with proportionate tachycardia ; pains in the limbs are less constant. Shivering is common ; rigors in adults or convulsions in children are occasional events. Cough and bronchitis are not unusual, nor is sore throat, which, however, as Marsden explains, is strictly not a toxæmic symptom but connected with the appearance of the enanthem upon the palate and fauces.

Prostration is marked, and Ricketts drew attention to the characteristic greyish fatigued expression of the face—due to

loss of tone of the small muscles—which Wanklyn aptly described as having an "ironed-out" appearance. The conjunctivæ may be suffused. The tongue is furred, the mouth dry and the breath offensive. Although physically prostrated, the patient may be at this stage mentally alert; too alert, since insomnia is not infrequent. Delirium of violent type may occur. On the other hand, in a small proportion of cases symptoms pointing to toxic encephalitis may be present, and in Marsden's series (*v. minor*) these symptoms varied "from extreme drowsiness and mental confusion to complete loss of consciousness." He remarks that "the most characteristic feature of this syndrome is its rapid and complete disappearance at the termination of the toxæmic stage and the appearance of the focal rash (*vide infra* encephalomyelitis). The duration of the initial toxæmia is very variable but most important to observe in connection especially with the differential diagnosis of chickenpox (*q.v.*). The most common period is two or two and a half days, but periods of three days are not uncommon. Rarely, the initial illness may last not more than twenty-four to thirty-six hours.

Prodromal (Toxæmic) Rashes.—In a proportion of cases prodromal rashes occur. They are (i) *hæmorrhagic (petechial or purpuric)*: associated with toxic or hæmorrhagic smallpox and therefore indicative of a severe or fatal attack; (ii) *erythematous*: these may be subdivided into scarlatiniform, morbilliform and roseolar and tend to occur in association with mild attacks; (iii) *urticarial.*

Ricketts pointed out that the development of a few petechiæ is common and, "fortuitously arranged," do not constitute a purpuric rash. The typical petechial prodromal rashes, sometimes associated with erythemata, occur most constantly in the groins and may also be present in the flanks and axillæ. Owing to their hæmorrhagic nature they persist and may be seen in association with the focal eruption. But in such cases the patient may die before the eruptive stage has developed. Ricketts noted that the purpuric rash "has a tendency to shield from the invasion of the focal lesions those parts of the skin which it occupies." Although erythematous prodromal rashes may appear in other parts of the body, they occur typically and most abundantly in the bathing drawers area and disappear before the focal eruption. Occasionally, both petechial and erythematous prodromal rashes occur in the same patient. Urticarial prodromal rashes have been noted in *v. minor*.

(*b*) *Eruption*: (1) *Character of the Lesions* (*vide* Fig. 25).—

In their earliest stages the focal lesions of smallpox are *macular* and not raised above the surface of the skin. These macules, of pin-head size, have been likened to "angry flea bites," lacking, of course, the central puncta. In a few hours the macules have become definitely papular. The *papules* are deep-set in the skin, dark pink in colour, $\frac{1}{8}$ in. or more in diameter and "shotty" when rolled between finger and thumb. Surrounding each lesion is an areola of lighter pink and of variable width. Papules continue to appear until the eruption of the papular stage is complete. This process occupies two, sometimes three, days. Then the conversion of papules into vesicles commences with those lesions which were the earliest to appear. The breaking down of the solid papule commences at the top, and in twenty-four hours or so all have become clear vesicles. For the first twenty-four hours they remain clear and then become turbid. The early vesicle is plump and well filled, the apex usually being rounded but sometimes flat. The plan is circular, not elliptical, the diameter being $\frac{1}{4}$ in. or less. During the later stage a variable proportion of the vesicles show the phenomenon known as "umbilication," a dimpling of the apex due to loss of fluid tension. Although of no great practical importance, and subject to exceptions in children and in cases of *v. minor*, the vesicle can be shown to be *multilocular*; pricked with a needle it fails to collapse entirely (as it does in chickenpox) because fluid is not released from all the chambers. The areola present in the papular stage increases in width and attains its maximum during the first twenty-four hours of the vesicular stage.

The vesicular stage lasts about two days and then merges into the pustular stage, which lasts about four days. During the first two days of this stage the vesicles, at first turbid, become definite *pustules*, and during the last two they become enlarged and may reach a diameter of $\frac{3}{8}$ in., when they attain the stage of *maturation*. By this time the areola has *disappeared*.

During the ensuing eight or nine days the pustules gradually dry up, forming, ultimately, dark brown, almost black, scabs or "seeds" which take a variable number of days to separate. On the palms and soles many days may elapse before separation is complete. Circular scars are left; the bases of these are at first pigmented, but they ultimately become avascular cicatrices or "pocks."

(2) *Order of Appearance and Distribution*.—1. *Enanthem*.—The earliest focal lesions to appear are those upon the buccal, faucial, pharyngeal and bronchial mucosa. Subjective evidence

of their presence may be, as already noted, the patient's com plaint of sore throat, but they may also be surmised from the occurrence of hoarseness and cough. The lesions of the enanthem vary very greatly in point of numbers in individual

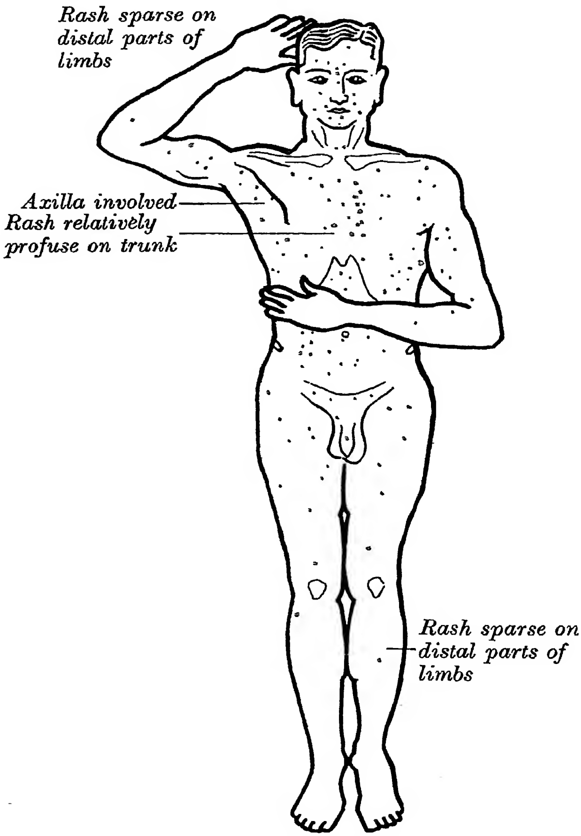


FIG. 27.—Chickenpox showing Centripetal Distribution of the Rash.

cases and do not necessarily bear any relation to the density of the lesions upon the skin. Owing, probably, to the delicate nature of the structures upon which they occur, evolution tends to be more rapid than in the case of the cutaneous lesions, and they may be seen at a later stage than the latter upon the

hard and soft palate, the fauces and, sometimes, upon the edges of the tongue. Since the existence of lesions in the mouth may be an important point in the differential diagnosis of doubtful cases, their presence should always be sought.

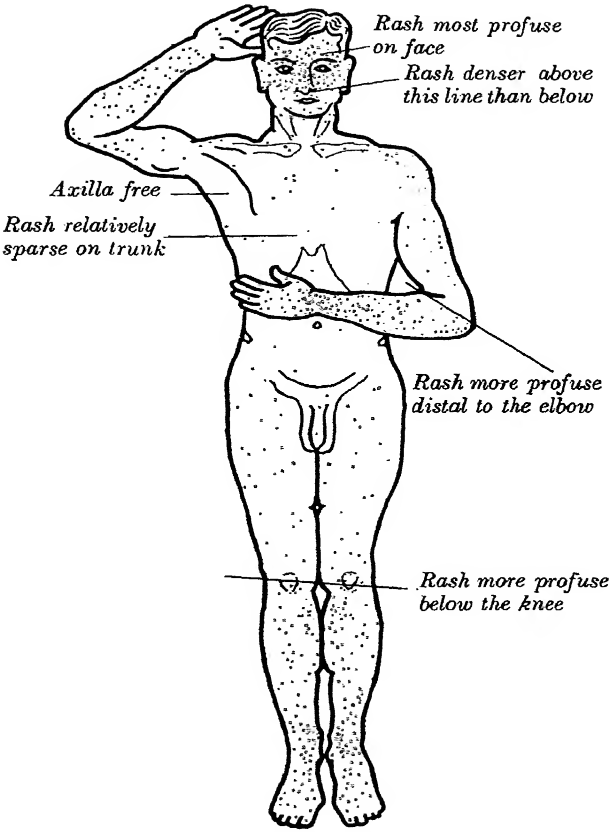


FIG. 28.—Smallpox showing **Centrifugal** Distribution of the Rash.

2. *Exanthem.*—The cutaneous lesions first appear upon the forehead and, variably, upon the scalp. Sometimes lesions are to be seen early upon the wrists also.

It is essential to observe the *regional order* of appearance of the lesions and their *relative density* in the various anatomical

divisions of the body, and to compare *proximal* with *distal* profusion. The order of appearance of the lesions of smallpox and their distribution are so characteristic as to be almost pathognomonic.

(i) *Order of Appearance and Density.*—The *face* is first invaded; then the *arms*; next, the *trunk*, particularly the *back*, and lastly, the *legs*. The density of the lesions is always greater upon the *face* and upon the *arms*.

(ii) *Centrifugal Distribution.*—In his classical studies Ricketts showed that the eruption when fully developed presents a typical *centrifugal* distribution (*cf.* the *centripetal* distribution of *chickenpox* in Chapter XXI). Thus although every anatomical region of the body is commonly invaded in the order and density stated above, when any region is examined separately it is seen that the distal parts bear a relatively greater profusion of lesions than those which are proximal. Upon the trunk, especially upon the chest and abdomen, lesions are scanty or relatively scanty; upon the face they are numerous, but if an imaginary line be drawn through the nostrils they are seen to occur more profusely above than below this line, *i.e.*, the lesions are centrifugal. Upon the *forearms* and *hands*, extending to the very tips of the fingers, lesions occur more profusely than upon the *upper arms*, and the same is true of the *thighs* as compared with the *legs* and the *feet*. Lesions are more numerous upon the *extensor* than the *flexor* aspects of the limbs. Another point of importance, taught by Ricketts, is the tendency for the lesions to occur upon *convexities* and *prominences*, again the exact opposite of chickenpox where lesions are more profuse in *concavities* and *protected* parts. Thus in smallpox lesions will be found upon the brow and the prominences of the malar bone, the *cavity* of the orbit bearing relatively few lesions. The bridge of the nose, the point of the chin, the pinna, the prominence of the sternomastoid, the clavicle, the back of the neck and the scapula are usually the sites of lesions. In chickenpox, on the other hand, the cavity of the *axilla* commonly shows many lesions, whereas in smallpox lesions in the axilla are relatively scanty and sometimes absent.

Unusual Aggregations.—In smallpox, as in chickenpox (*q.v.*), areas or lines of pressure, irritation or inflammation existing during the incubation period tend to become the sites of aggregations of lesions of the focal eruption. The pressure lines of braces or garters, occupational pressure points upon the fingers, scratches or sunburn are examples. Extensive areas of sunburn upon the back or chest may thus result in

a blurring of the skin picture, although careful examination of the distribution as a whole reveals the essential symmetrical, centrifugal character of the eruption with its gradation of density from above downwards.

General Clinical Manifestations.—The symptomatology of the prodromal stage has already been described. With the

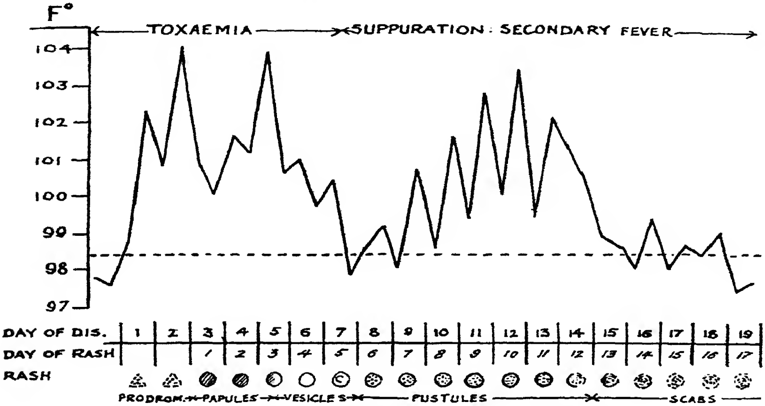


FIG. 29.—Unmodified *Variola major* showing Secondary Fever of Maturation.

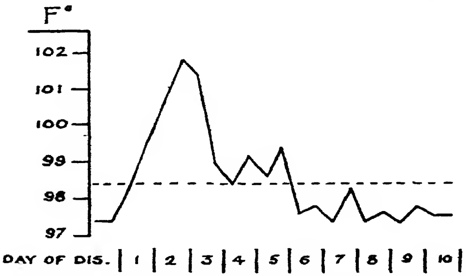


FIG. 30.—*Variola minor* without Secondary Fever.

appearance of the papular eruption the temperature falls and the patient's general condition improves. Towards the end of the vesicular stage and during the pustular stage the temperature rises again and the condition deteriorates as the result of septic absorption. The more profuse the eruption the more severe is this secondary fever likely to be, with enhanced danger from cardiac failure or pulmonary complications.

In *modified smallpox* and *v. minor* the secondary fever is as a rule of minimal proportions or fails to occur at all.

CLINICAL CLASSIFICATION OF SMALLPOX.—Attacks of *unmodified* smallpox vary greatly in clinical severity. The following classification is that of Ricketts (1893) :—

(i) *Hæmorrhagic* or *toxic*, based upon the severity of the primary toxæmia.
(ii) *Confluent* on the face : (*a*) in the papular or vesicular stage ; (*b*) in the pustular stage, at the time of maturation.
(iii) *Discrete* pocks on the face : (*a*) exceeding 500 ; (*b*) 100 but not more than 500 ; (*c*) not more than 100.

It will be observed that in *confluent* smallpox the lesions on the *face* are so closely set that at one stage or another they become contiguous. At the stage of pustulation the patient's features may become, for the time being, unrecognisable owing to the closeness with which the lesions are set and the concomitant œdema of the skin. The term *semiconfluent* is applied when only a proportion of the lesions are confluent. In *discrete* smallpox there are, at all stages, areas of skin between the facial lesions, *i.e.*, the latter are not contiguous.

Hæmorrhagic smallpox occurs in two forms : (*a*) *purpura variolosa*. In this form, included in the classification above, during the course of a prodromal stage of intense severity with a concomitant petechial prodromal rash, hæmorrhages occur into the skin generally and from all the mucous membranes. Death, which is invariable, may result before the appearance of the focal eruption or occur as this is beginning to appear. The papules are characteristically badly formed and velvety to the touch. (*b*) *variola hæmorrhagica pustulosa*. In this form the appearance of hæmorrhages is deferred until the late vesicular or pustular stages. It is not so invariably fatal as *purpura variolosa*.

Variola sine eruptions.—Smallpox confined to the initial toxæmia occurs in the previously vaccinated who have lost some degree of immunity to the toxin of the virus but who still retain skin immunity to the focal eruption. Occasionally a few small and atypical focal lesions may appear and possibly be overlooked.

Modified Smallpox (*Varioloid*).—This is the form which ordinarily occurs in lapsed immunes and, without qualification, means a modified attack of *v. major*. The prodromal illness may be severe and the focal eruption occasionally profuse, although, as a rule, both phases of the attack are mitigated.

The essential feature of modified smallpox is the *abortion* of a varying proportion of the focal lesions. They dry up in the stage of papulation or vesiculation; the papules also tend to be smaller than in the unmodified form. The clinical effect of this abortion of the lesions is the suppression or mitigation of the secondary illness due to septic absorption from the pustules.

V. minor, mild smallpox, alastrim, is smallpox modified by the lesser virulence of the infecting strain, although, be it said, not all cases of *v. minor* are mild. Toxic and confluent attacks have occurred, but these are exceptional. "Influenza with spots" is a terse but adequate description of the majority of the cases. The disease is essentially modified smallpox. The following characteristics should be noted because they may give rise to difficulties in diagnosis: (i) In the unvaccinated the attack is usually mild; the mortality is trifling. (ii) The incubation period may be prolonged (*vide supra*). (iii) The prodromal stage usually, but not invariably, is of slight severity and accompanied, rarely, by erythematous or urticarial prodromal rashes. The severity or otherwise of the prodromal stage is not a reliable indication as to the probable profusion of the focal eruption. (iv) The lesions tend to *appear* in a more leisurely fashion but to *evolve* more rapidly. Thus papules may erupt upon the face twenty-four hours before those upon the arms. Sometimes, as in chickenpox, papules may appear first upon the back and chest. Once having appeared, the lesions hurry through the stages of vesiculation and pustulation, but few or many may abort in the papular stage. The occurrence of "crops" of lesions, the abortion of some and the rapid maturation of the others are factors which may give rise to confusion with chickenpox (*vide* Chapter XXI), *but the distribution of the lesions is precisely that of smallpox, viz., centrifugal.* As in modified *v. major*, owing to the abortion of lesions, the secondary fever is either slight or absent. Complications are few and deaths rare.

Complications.—Complications may arise from the effect of the virus itself or from the secondary bacterial invasion of tissues damaged by the virus.

1. *Cardiac.*—Myocardial failure may occur during the stage of toxæmia in the toxic or hæmorrhagic forms, or during the secondary illness which accompanies maturation of the pustules. Bacterial invasion of the endo- or pericardium is rare.

2. *Nervous.*—Apart from delirium or convulsions "nervous symptoms varying from extreme drowsiness to complete loss

of consciousness, and probably due to toxic encephalitis, may occur at the commencement of the illness and disappear completely at the termination of the toxæmic phase" (Marsden).

Encephalomyelitis (*acute perivascular myelinoclasis*) is pathologically identical with *post-vaccinal encephalitis* (*vide infra*). It occurs from five to thirteen days after the appearance of the focal rash. Marsden and Hurst (1932) differentiate two types according to the relative intensity of encephalic or spinal symptoms. In the first type the most prominent feature is disturbance of speech, which improves only very slowly. The condition usually appears as the patient recovers from the mental disturbance of the toxæmic stage. In the second type paralysis of the limbs with or without sphincter disturbance is the outstanding feature and many cases of this type prove fatal. "The two types may overlap and the distinction is rarely clear-cut" (Marsden and Hurst).

Other nervous complications, *e.g.*, *peripheral neuritis* and *psychoses*, occasionally occur.

Respiratory.—A certain degree of bronchitis with or without laryngitis is usual in the more severe attacks. *Bronchopneumonia* and less commonly *lobar pneumonia* may be terminal and fatal events.

Special Senses.—(i) *Eyes*.—Simple conjunctivitis is common at the onset; it subsides with the waning of the toxæmic stage. As in chickenpox, focal lesions may occur upon the conjunctiva. If they appear upon the ocular conjunctiva they may become secondarily infected with resulting keratitis and destruction of the globe. In this case, excision of the affected globe is necessary in order to prevent the occurrence of sympathetic ophthalmia.

(ii) *Ears*.—*Otitis media* is an occasional extraneous complication.

Genito-urinary.—The pregnant woman may *abort* at any stage of an attack of smallpox, and disturbances of *menstrual function* are not uncommon. *Orchitis* is an occasional complication.

Skin.—Pustular dermatitis and boils may be troublesome in convalescence.

Diagnosis.—1. PRODROMAL STAGE.—In the absence of a definite history of exposure of an unvaccinated person or the occurrence of a distinctive petechial prodromal rash, a diagnosis of smallpox in the toxæmic stage is usually impossible. On the other hand, a recent history and *evidence*, in the form of foveated scars, of vaccination may *exclude* a diagnosis of

smallpox. This evidence should always be sought first in any suspected case. (The possibility of vaccination having been performed upon unusual sites should always be borne in mind.)

Especially in *v. minor* the associated catarrh and bronchitis in the prodromal stage may be mistaken for "influenza." The following conditions may simulate, more or less, the prodromal stage of smallpox and, during an epidemic or in an endemic centre of the disease, be mistaken for it: lobar pneumonia, cerebrospinal fever, enteric fever, malaria and exanthematic typhus. Usually before the appropriate bacteriological, hæmatological and serological tests can be completed the disease declares itself by the appearance of the focal eruption.

2. ERUPTIVE STAGE. — *Method of Examination.* — Many mistakes in the diagnosis of smallpox arise from an unsystematic examination of the eruption. It is essential that the light should be good; daylight is far preferable to artificial light. The clothes should be removed as far as possible and the patient, wrapped in a blanket, placed upon a couch or bed. The examiner first inspects the state of vaccination, and this in itself may be sufficient to exclude smallpox (*vide supra*). Next, the fauces and buccal cavity are examined for the presence of lesions. The blanket is then opened out and the patient directed to fold the arms across the chest. Then the examiner, standing at the foot of the bed, observes the general and relative distribution of the eruption. Particular attention is paid to the gradations of density of the lesions upon the face, arms, trunk and legs; to the arrangement of the lesions in a centrifugal, centripetal or haphazard manner; and to their profusion or otherwise upon prominences or in hollows respectively. Only when these features have been determined should attention be paid to the character of individual lesions.

The following conditions are among those likely to be confused :—

(*a*) *Chickenpox.*—Distribution centripetal; lesions in all stages; vaccinal state irrelevant (*vide* Chapter XXI, Chickenpox).

(*b*) *Measles.*—In the early stages the velvety maculopapules upon the forehead in severe cases of measles may be mistaken for the similar velvety lesions in toxic smallpox, but the presence of Koplik's spots and the subsequent evolution of the eruption are conclusive of measles (*vide* Chapter XVI, Measles).

(c) *Skin Diseases.*

(i) *Children : papular urticaria ;* lesions absent or sparse upon the face ; never present in the mouth ; tendency to abundance around ankles. Lesions are small superficial papules, some with minute conical vesicles at summit and with a surrounding erythema which later fades leaving the papules. Sometimes wheals may be found. There are usually scratch marks and frequently evidence of old lesions. The child is usually in good health.

(ii) *Adolescents : pustular acne.* Distribution upon face, back and upper chest. The skin is greasy, with comedones (blackheads) and usually abundant evidence of scarring as the result of chronicity.

(iii) *Adults : pustular syphilides.* Distribution not centrifugal ; usually pustular from commencement, but papules may be seen mixed with pustules. Other signs of syphilis and W.R. serve to distinguish. Note the possibility of concurrent smallpox and syphilis.

(iv) *Erythema multiforme* of bullous type is sometimes confused. Large superficial bullæ appear, particularly upon the backs of the hands and upon the legs ; less abundant upon the face. Bullæ are usually combined with lesions of other types characteristic of the disease.

(v) *Drug Rashes : iodides, bromides* and *copaiba.* There is a history of administration of the drug and the distribution does not conform. Note the sequence of backache, for which " backache and kidney " pills may be taken, and the appearance of a morbilliform eruption due to copaiba or some other oleoresin contained in the pills.

SPECIFIC METHODS OF DIAGNOSIS.— *Vaccination* has already been mentioned. Even in the unvaccinated, vaccination performed after the commencement of the attack of smallpox fails to take.

Flocculation Test.—Based upon the observations of Mervyn Gordon (1925), who demonstrated by means of complement-fixation and flocculation tests that the viruses of variola and vaccinia were serologically identical. Burgess, Craigie and Tulloch (1929) devised

a diagnostic test. A rabbit-vaccinia-flocculating serum is added in various dilutions to tubes containing a saline extract of the scabs derived from lesions of the suspected case. The occurrence of flocculation after incubation is evidence that the scabs were those of smallpox lesions. The test is thus only of retrospective value for the clinician, since crusts and scabs are available only towards the end of the attack. For the investigation of an outbreak which may have been regarded as chickenpox the test has obvious utility.

Paul's Test.—Of very limited value to the clinician, this test consists in the inoculation of an area of the cocainised cornea of a rabbit with matter derived from a vesicle or pustule of the suspected case. Two days later the animal is killed; both globes are excised and immersed in mercuric chloride and alcohol. Examination of the "control" cornea shows an even opacity; that of the inoculated cornea, if the material inoculated was derived from a case of smallpox or vaccinia, dense white and opaque elevations set upon a milk-white background. Suitable methods of examination may reveal the presence of the inclusion bodies of Guarnieri.

Prophylaxis. — (1) **Vaccination.** — The rational and only efficient method of preventing smallpox in a community is the production of active immunity to the disease by means of an artificially acquired attack of vaccinia, *i.e.*, by vaccination.

Variolation.—The forerunner of vaccination was the procedure of ingrafting, inoculation or variolation introduced into England by Lady Mary Wortley Montagu from Turkey in 1721. This consisted in scratching into the arm of the person to be variolated matter from smallpox pustules. The desired result was a mitigated attack of smallpox and thus permanent protection. But sometimes fatal attacks ensued and, in any case, the subject, during the attack, was infectious to others. Variolation, in time, became popular, but it waned with the introduction of vaccination, and ultimately, in 1840, was made illegal in this country.

Vaccination.—Edward Jenner of Gloucester introduced vaccination in 1796. The procedure was based upon his observations that dairymaids, although liable to contract cowpox from infected animals, did not, after an attack of this disease, develop smallpox following exposure. Jenner put these observations to an experimental test by inoculating a boy with the matter from cowpox pustules as the result of which he contracted cowpox. Subsequent variolation was unsuccessful. He thus concluded that cowpox in the human being protected against smallpox. Jenner's conclusion has been abundantly upheld all over the world, but his belief that

the immunity afforded was as solid as that afforded by an attack of smallpox and that it endured for life has not proved to be correct. As in all other processes of artificial immunisation subsequently introduced, *re-vaccination* at intervals of years is necessary in order to maintain the level of immunity.

As already stated, the virus of vaccinia is essentially the same as that of variola (*vide supra* Causal Agent), but "its virulence for man, not its immunising action against variola, has been modified by passage through the cow" (Mervyn Gordon). Calves and rabbits are susceptible to vaccinia virus; inoculation produces upon the shaved skin of calves a papule which subsequently becomes vesicular and pustular. The vesicles contain the Paschen bodies.

Vaccinia virus for human vaccination is produced by inoculating lightly made parallel linear incisions upon the shaved belly of the calf with virus which has been obtained from lesions produced in the rabbit. Upon the fifth day the contents of the vesicles which have formed are scraped off. The *pulp* so obtained is mixed with glycerin and saline containing a preservative, triturated to make a smooth emulsion and after cold storage which effects a reduction in the number of skin organisms the product is filled into capillary tubes and issued as calf lymph to vaccinators. Thus calf lymph is not bacteriologically sterile; in addition to the living virus it contains some skin organisms.

During the last few years successful attempts have been made by Goodpasture and others to grow the virus free from extraneous organisms upon the chorio-allantoic membrane of twelve-day chick embryos. The egg is opened four days later and the membrane is then found to be studded with opaque plaques which contain the virus in abundance. The plaques are excised and after grinding in the frozen state and the application of sterility tests are diluted to form "lymph." The potency may exceed that of calf lymph. There is no evidence of increase of neurotropic affinity of the virus (W. D. H. Stevenson and G. G. Butler, 1939).

It seems probable that the virus so prepared will ultimately supersede calf lymph.

TECHNIQUE OF VACCINATION.—1. *Age.*—The best time at which to perform *primary* vaccination is between the ages of two to six months. Performed in infancy the likelihood of post-vaccinal encephalitis (*vide infra*) is much reduced. *Re-vaccination* is desirable at the time of school entry, *i.e.*, at five to seven years of age, and again when the child leaves school, between the ages of fourteen and sixteen years.

2. *Number of Insertions.*—At one time it was customary to make four insertions of lymph with a view to securing

immunity for the maximum period. Since the duration of the protection afforded is proportionate to the area of true foveated (pitted) scarring, the aim was to produce an area of vesiculation of at least half a square inch. Solid immunity for seven years could be reasonably counted upon, although the period might be either shorter or longer.

The general decline in the acceptance of vaccination, accelerated by the very occasional occurrence of nervous sequelæ and especially by the appearance of a mild type of smallpox, influenced the Committee on Vaccination to recommend a modified technique which would tend still further to reduce the incidence of post-vaccinal encephalitis and would be more readily accepted by the public. The Vaccination Order of 1929 directs Public Vaccinators to make a *single linear* insertion with the minimum of trauma ; scarification and cross-hatching are both deprecated. The duration of the immunity conferred by a single insertion is not yet established, and there is, of course, no objection to private practitioners making more than one insertion when it is desired to secure immunity of maximum duration. It is to be borne in mind, however, that even with four insertions the duration of absolute immunity varies in different people. Ricketts considered that the *minimum* duration of absolute immunity was two years.

The *lymph* used by Public Vaccinators is issued by the Government Lymph Establishment. Lymph from proprietary sources must comply with the requirements of the Therapeutic Substances Regulations of 1927. As issued, Government lymph is diluted 1 in 5, although 1 in 20 dilutions have given excellent results. It is essential to use fresh lymph ; if not used immediately after receipt it must be stored in a refrigerator, otherwise potency is soon lost. The only *instrument* required is a sterile round-pointed sewing needle. Scalpels and scarifiers are objectionable. The usual *site* for vaccination is over the left deltoid, but an area upon the inner side of the arm just above the inner condyle of the humerus is convenient (Goldberger's method). If a scar is objected to, the leg or chest may be chosen.

The *skin* is *prepared* by washing with soap and water followed by spirit. It is essential to avoid the use of a non-volatile antiseptic which would render the lymph inert. Time must be allowed for the prepared site to dry completely before insertion of the lymph. Usually the lymph is applied first, but if preferred may be rubbed gently into the scratch or puncture.

The common method of *ejection* from the capillary tube is to break off both ends and then to attach a rubber ejector to one end. By pressure one or more drops are expelled on to the skin. Then through the drop of lymph a superficial scratch is made, of $\frac{1}{8}$ in. in length, with the needle, *without drawing blood.* The scratch should not exceed $\frac{1}{4}$ in. There are two other methods of insertion either of which may be recommended.

In the *multiple puncture method* eight to ten superficial needle-point punctures are made through the drop of lymph over an area not exceeding $\frac{1}{8}$ in. in diameter. The *intradermic method* (E. R. Pierce, 1937, *B.M.J.*, i., 1066) is simple, speedy and efficient. Pierce uses as an ejector a soft rubber baby's feeding-bottle teat. The capillary tube, unbroken, is thrust through the small hole in the teat until about an inch is visible; the tip projecting from the base of the teat is broken off and the tube withdrawn into the teat until about an inch remains inside. Finally, the other tip of the tube projecting through the teat-hole is also broken off. By means of gentle pressure with the thumb over the open end of the teat "successive and discrete minute quantities of lymph can be expressed." The technique of insertion is that of the Schick test; the solid needle is held almost parallel with the skin and the point is inserted gently through the drop of lymph for about $\frac{1}{16}$ in., thus carrying a minute quantity of lymph into the skin on the point of the needle. It is not necessary to rub in superfluous lymph nor is any dressing required. "If the lymph is potent and the technique correct a specific reaction never fails to appear."

In the other methods described it is customary, after a few minutes, to apply a sterile dressing of lint and to secure it with a bandage in preference to strapping, which is liable to irritate the infant's skin.

Clinical Course of Vaccinia.—*Including* the day of vaccination the *incubation period* is three days, during which there may be an inflammatory reaction, reddening and itching, in part due to trauma (very much minimised by modern methods of insertion). On the *third day* there is a definite flush round the insertion.

On the *fourth day* a papule appears which on the *fifth day* has become a vesicle surrounded by an inflammatory *areola.* On the *sixth day* the vesicle shows *umbilication.* The clear vesicle during the *seventh and eighth days* becomes turbid and the areola increases in width and intensity. Pustulation occurs from the *eighth to the tenth days* and is associated with

an area of infiltration, intense itching and enlarged and painful axillary glands. Thereafter for the next two or three days infiltration increases, but the pustule commences to dry and shrivel. Later, infiltration and lymphadenitis subside and a brown scab is formed which separates in two or three weeks leaving a pigmented scar which ultimately becomes a foveated cicatrix or pock. *Constitutional disturbance* varies with the age of the vaccinee and the number of insertions. In the newborn, clinical symptoms may be negligible; in older infants slight pyrexia is the rule from the commencement of the vesicular stage, and irritability and restlessness due to the local inflammatory reaction are usual. In older children and adults constitutional disturbance during the late vesicular and pustular stages may be considerable, especially if multiple insertions have been made. *Splenomegaly* has been recorded in infants and as occurring in about two-thirds of a series of young adults; the condition, which is evident on or about the eighth day, produces pain and discomfort in the left side.

Re-vaccination is characterised by a speeding up of the evolution of the lesion and by very much diminished constitutional disturbance.

The greater the degree of residual immunity from primary vaccination, the less pronounced are the phenomena of re-vaccination. If the re-vaccinated person is still immune to vaccinia the only result is the appearance of a small itching papule which thereafter aborts. This is the *papule of immunity* of Pirquet.

Permanent scarring may not result from re-vaccination.

Generalised Vaccinia.—Rarely, crops of lesions appear upon the body generally and undergo the same evolution as the local lesions. The condition may be confused with smallpox, chickenpox or some skin disease; indeed, generalised vaccinia has been reported as occurring especially among those who already have some skin condition. The lesions appear at the height of the local process, but the distribution tends to be haphazard and does not conform with that of the lesions of smallpox, although, as in chickenpox, lesions are prone to occur upon the back.

Extraneous Lesions may be produced by scratching the vaccination site followed by autoinoculation of some other area of the body, *e.g.*, nose, ear or lips.

Vaccination after Exposure to Smallpox.—Although exceptions occur, Ricketts taught that vaccination done within a day or two of exposure prevents the attack with certainty. If, he said, the duration of incubation to the outcrop of the

rash be taken as fourteen days, and if this period be divided into three intervals comprising seven days, three days and four days, then, in the main, successful vaccination done in the *first* interval will wholly prevent ; in the *second*, modify, more or less ; but in the *last* " will merely add to the patient's troubles."

CONTRAINDICATIONS.—Vaccination is so beset by opponents that it is important to note the contraindications. Except in the emergency of known exposure to *v. major*, only healthy infants should be vaccinated ; if the infant is not in good health vaccination should be postponed. Congenital syphilis and active tuberculosis are contraindications, except in emergency. Skin diseases, such as eczema and impetigo, and recent exposure to any of the acute specific fevers dictate postponement.

COMPLICATIONS.—*Erysipelas* and *cellulitis* are the avoidable results of infection of the site by the fingers of child or mother or premature removal of the dressing. The latter should not be disturbed until the eighth day, when the arm is first inspected by the vaccinator who re-dresses the arm, and at his final re-inspection upon the fifteenth day removes the dressing.

Post-vaccinal Rashes may occur from the ninth day onwards and may be scarlatiniform, morbilliform or urticarial. They are of no significance and fade away in two or three days.

Post-vaccinal Encephalitis.—About the year 1923 evidence began to accumulate of the occurrence of nervous sequelæ associated with *primary* vaccination. The clinical manifestations and histological appearances of the lesions of the central nervous system were found to be identical with those met with in encephalitis following some of the exanthemata, notably measles (*vide* Chapter XVI). Subsequent experience has shown that the approximate incidence of this complication is of the order of one in a million vaccinations. J. F. M. Scott (1932), in an analysis of 569 cases at all ages, found that 41 (7·2 per cent.) occurred in infants under one year of age. No cases, so far, have been recorded in infants under one month; extremely few under three months and but few more under six months of age (L. O. Travis, 1938). All experience has shown that the majority of cases have followed the *primary* vaccination of children of school age and adolescents.

The Committee on Vaccination (1928) came to the tentative conclusion that, although some held the view that encephalitis following the exanthemata was due solely to the particular virus concerned, the alternative explanation that the co-operation of

vaccinia with the viruses of poliomyelitis or of encephalitis lethargica or possibly some unknown neurotropic virus harboured by the vaccinee must, for the present, be retained as a working hypothesis.

The case-fatality rate is about 50 per cent.

The condition has arisen as early as the seventh day after vaccination, but the *usual time of onset* is between the *tenth and twelfth day*. The onset is *abrupt* with headache, vomiting, pyrexia and lethargy. The condition may abort at this stage or the child may die in coma. In the more severe attacks convulsions, delirium, myoclonus and incontinence occur. The clinical appearance may suggest meningitis. Kernig's and Brudzinski's signs may be present, but variability of the reflexes from day to day is characteristic. Lumbar puncture reveals a clear fluid under pressure (*vide* Chapter XXIII). Residual paralyses at first spastic and then flaccid (*cf.* poliomyelitis) and mental impairment occur in a proportion of recovered cases, but more usually the child dies in coma or recovers without residual damage.

Treatment.—Success has attended the injection of serum or whole blood derived from recently vaccinated persons. Horder (1929) injected intrathecally 5 c.c. of the serum of the recently vaccinated mother; Hekman (1930) injected intravenously, and repeatedly if necessary, 10 c.c. of similar serum. Sakochansky and Trenchard (1939) report the cure of an infant of fourteen weeks following the *intramuscular* injection of 10 c.c. of the mother's *whole blood* and 10 c.c. of the *whole blood* obtained from a youth of seventeen who had been vaccinated four weeks previously with the same batch of calf lymph. Horse-antivaccinal serum has also been prepared.

Other Nervous Complications attributed to vaccinia, such as *convulsions*, possibly due to tetany, and *bacterial meningitis*, are to be regarded as fortuitous.

(2) **Control of an Outbreak of Smallpox.**—The practitioner who diagnoses smallpox or suspects that the condition may be smallpox must at once communicate with the appropriate medical officer of health. The M.O.H. should observe, *inter alia*, the following procedure, which is advised by the Ministry of Health (Memo. $\frac{215}{\text{Med.}}$ 1938):—

(i) Visit the patient with the practitioner with a view to confirming the diagnosis.

(ii) If the diagnosis is confirmed, the patient should at once be removed to a smallpox hospital.

(iii) Vaccination or re-vaccination should be offered to all contacts. (The M.O.H. is himself empowered to vaccinate under Public Health (Smallpox Prevention) Regulations (1917).) (*Vide supra* Vaccination.)

(iv) Contacts should be kept under medical surveillance for a period of *sixteen days* after the last exposure to infection. For this purpose it is seldom necessary or desirable to isolate them in their homes.

(v) The infected house and its contents, together with the clothing of all persons known to have been in close contact with the patient, should be disinfected. In the case of *v. minor* a less stringent standard of disinfection may be adopted at the discretion of the M.O.H.

The *period of isolation* of a patient suffering from smallpox is determined by the time taken for the *complete* separation of the scabs and the formation of dry, healed cicatrices. *Concurrent* and *terminal* disinfection in smallpox wards is essential. All attendants, medical, nursing and lay, must be vaccinated or re-vaccinated.

Special administrative precautions are necessary to obviate the transference of infection by the staff to the community. These include the wearing of protective gowns, including hoods, when nursing. The hoods prevent the adherence of scabs, detached from patients, to the hair. Arrangements are made to discard these garments when leaving the ward. Special living and sleeping quarters are provided and the staff for the time being is virtually interned within the curtilage of the hospital. Precautions are taken to prevent the ingress of unauthorised persons to the hospital; any permitted to enter must be protected by vaccination. In the case of *v. minor*. the precautions may be less stringent, but if *v. major* is in question they must by no means be relaxed.

Treatment.—The treatment of the smallpox patient consists largely in skilled nursing. As much rest as possible is essential because of the effects of the disease upon the myocardium. At the same time, regard to posture is most important because of the liability to pulmonary complications and to pressure sores. A mattress of the "sorbo" rubber type is preferable to the ordinary form. Continuous attention to the hygiene of the mouth, eyes and skin is essential. Owing to the liability to delirium of violent type and the tendency of the smallpox patient, in his delirium, to break out of the ward and possibly scale the wall, sufficient assistance must always be available to impose the necessary restraint.

The headache and pains in the back and limbs of the

toxæmic stage may respond to drugs such as aspirin, but may necessitate an injection of morphine; and while restlessness and the milder grades of delirium may be controlled by chloral and bromides or paraldehyde, an injection of hyoscine may be called for. The condition of the heart must be ascertained frequently and cardiac drugs such as coramine prescribed if necessary.

The skin lesions in the pustular stage give rise not only to great discomfort to the patient but to an objectionable odour. It is important, therefore, to lessen the degree of pustulation and to mitigate its effects by any means available. Promising results in this direction have been reported from the use of sulphonamides given early as a prophylactic against the secondary infection (*not* the virus), but these drugs must be employed with the usual precautions. A solution of permanganate of potash is frequently applied upon a swab to individual lesions, the treatment being commenced in the papular stage.

In chickenpox we have found Mitman's paint (*vide* p. 249) superior to potassium permanganate in lessening the effects, *i.e.*, the scarring, which may follow pustulation and scabbing, but so far we have had no experience of its use in smallpox. Repeated bathing of the pustules with an alkaline lotion containing some deodorant is comforting to the patient and his attendants alike.

Although the separation of the scabs may be facilitated and to some extent hastened by treating each lesion with a feather dipped in camphorated oil, separation must not be effected by force, since the traumatic lesion which may result sometimes takes a longer time to heal than that occupied by the separation of the scab in the ordinary way.

Convalescence from smallpox may be protracted and after release from isolation a prolonged period of rest, fresh air and tonic treatment is desirable.

SUMMARY OF CHAPTER XXII

Causal Agent: Virus (Paschen bodies) identical with that of vaccinia.

Clinical Features: Prodromal toxæmia; focal eruption (centrifugal), complications.

Diagnosis: From chickenpox, measles, skin diseases and drug rashes.

Prophylaxis: Specific; vaccination. General; isolation, disinfection and surveillance of contacts.

Treatment: Nursing and symptomatic.

CHAPTER XXIII

ACUTE INFECTIOUS DISEASES OF THE NERVOUS SYSTEM

GENERAL Characteristics.—The diseases considered here are grouped together because they affect the same anatomical structures—the nervous system. They have, however, other points in common. With few unimportant exceptions they follow upon an infection of the respiratory tract, *i.e.*, they are primarily *inhalation* diseases. It is of interest to note the part that filterable viruses play in these diseases. In acute infections of the nervous system there is a tendency for all structures to be involved, but in some of them the main incidence of the disease is upon the meninges (*meningitis*), in others it is upon the substance of the brain and spinal cord (*encephalomyelitis*). Most cases of meningitis are due to *bacteria*, whereas encephalomyelitis is almost always due to *filterable viruses* which, because of their affinity for nervous tissue, are grouped as neurotropic.

The acute infections of the nervous system may be divided into those in which the involvement of the nervous system is the usual, indeed a characteristic, feature, and those in which it is an unusual complication of a disease whose characteristic symptoms are located in some other systems.

Thus the chief acute infections of the nervous system may be classified as on Table XVII.

The classification in Table XVII is not rigid. Benign lymphocytic meningitis is a viral disease; mumps, a virus disease, is occasionally complicated by meningitis; whooping-cough and scarlet fever, both bacterial diseases, occasionally cause encephalomyelitis; hydrophobia, an encephalomyelitis due to a virus, is an inoculation disease; and typhoid fever, an ingestion disease occasionally causes meningitis; but those in the list are most important.

In encephalomyelitis, although the central nervous system is diffusely affected, the involvement is seldom uniform. If the preponderance of pathological change is upon the brain, the condition is an *encephalitis*, as in epidemic encephalitis; if upon the spinal cord, a *myelitis*, as in acute poliomyelitis.

TABLE XVII

	Involvement of the Nervous System a Characteristic Feature *	**Involvement of the Nervous System a Secondary Complication**
Bacterial infections causing **meningitis.**	Meningococcal meningitis	Pneumococcal meningitis. Streptococcal meningitis. Tuberculous meningitis.
Viral infections causing **encephalomyelitis.**	Acute poliomyelitis (or polio-encephalitis) Epidemic encephalitis	Encephalomyelitis complicating : Measles, Vaccinia, Smallpox, Chickenpox, Influenza.

* These constitute the chief epidemic diseases of the nervous system.

In those diseases in which encephalomyelitis is a characteristic feature, *e.g.*, epidemic encephalitis, poliomyelitis and rabies, the *grey* matter is chiefly involved. In the encephalomyelitis, which is a complication of the infectious diseases, such as that following measles, vaccinia, smallpox, chickenpox and influenza, although the grey matter is affected, the main incidence is upon the *white* matter, which shows in all these diseases a *perivascular demyelination*, *i.e.*, there is a loss of the myelin sheath in the nervous tissue around the blood vessels. Instead of such diffuse lesions, it sometimes happens that the damage is localised, causing a focal nervous lesion such as paralysis of a limb or a group of muscles.

In addition to *infections* of the nervous system there are *intoxications*. In every infectious disease in which there is an appreciable toxæmia, the nervous system may be diffusely affected, and such cerebral symptoms as convulsions, delirium, restlessness, sleeplessness, drowsiness, stupor and coma may result. There are, however, two important intoxications of the nervous system—those due to *diphtheria* and *tetanus*—in which there are characteristic nervous symptoms. In both an

exotoxin travels from the site of the local infection along the peripheral nerves to the central nervous system. Influenza and dysentery may also affect the peripheral nerves.

Convulsions are a common symptom of nervous involvement. The following is a list of the commonest causes in children, in so far as they enter into the differential diagnosis of infectious diseases :—

1. Any acute specific fever at the onset.
2. Cerebral diseases :
   (*a*) Meningitis.
   (*b*) Encephalitis, or encephalomyelitis.
   (*c*) Tumour, abscess, etc.
3. Epilepsy.
4. Whooping-cough.
5. Diseases associated with alteration of alkali and calcium metabolism :
   (*a*) Tetany.
   (*b*) Rickets.
   (*c*) Diarrhœa and vomiting (enteritis).
6. Secondary to sources of irritation, *e.g.*, dentition, worms, phimosis, colitis, etc.
7. Idiopathic.

Convulsions appear to be less common at the onset of the infectious diseases than they were formerly; this may possibly be due to the greater rarity of rickets and the associated tetany.

Delirium is usually evidence of a severe toxæmia and is not a common symptom of infectious diseases ; the violent *maniacal* type is rare, although minor degrees of disturbance, such as restlessness and attempts at getting out of bed, are not infrequently seen, particularly in older patients. In profound toxæmias, such as those which occur in enteric fever, puerperal septicæmia, pneumonia and meningitis, the *low muttering* type of delirium is more common. The patient lies still and sunken in the bed, and mutters incoherently.

The Chief Epidemic Diseases of the Nervous System—cerebrospinal fever, poliomyelitis and epidemic encephalitis—have certain common epidemiological and clinical features, so that diagnosis is sometimes difficult. In the past confusion has occurred, not only as to individual cases, but as to the character of the epidemic as a whole. All three may be transmitted by case to case contact, but often the association cannot be traced. Many links in the chain of transmission are missed, because

of the frequent occurrence of carriers and of mild and abortive cases. Thus during epidemics the organism is widespread among the population and the overt cases represent only a small proportion of those infected. There are, however, points of difference. The highest incidence of acute poliomyelitis is upon children under five years of age; of cerebrospinal fever, on children five to ten years of age; and of epidemic encephalitis, on adults of thirty years and upwards. Fatality is greatest in cerebrospinal fever and least in acute poliomyelitis. The latter is a disease of the late summer and autumn, whereas the other two occur in winter or early spring.

The *nervous manifestations* present points of similarity and of difference. In all of them the inflammatory process may, on the one hand, produce irritation or stimulation with increased activity, and on the other, depression of the functions of the nervous system, *e.g.* :—

	Signs of Irritation	**Signs of Depression**
Mental Process	Restlessness.	Apathy.
	Irritability.	
	Insomnia.	Drowsiness or lethargy.
	Noisy and troublesome behaviour.	Stupor.
	Delirium.	Coma.
Muscular Function	Spasticity or rigidity.	Flaccidity.
	Twitchings.	Paresis or paralysis.
	Spasms.	
	Convulsions.	
Sensory Function	Hyperæsthesia. *e.g.*, cutaneous or of special senses.	Anæsthesia.

In *cerebrospinal fever* the emphasis is upon irritability of muscular function resulting in stiffness; in *acute poliomyelitis* there is depression of the muscular function with flaccidity and paralysis; and in *epidemic encephalitis* there is commonly depression of the mental processes.

In all of them changes occur in the cerebrospinal fluid. In meningitis the departure from the normal appearances is most pronounced. In Table XVIII the changes are contrasted.

CEREBROSPINAL FLUID

Cerebrospinal fluid is produced by the choroid plexus, either by filtration from the blood or by secretion from the

cells of the plexus. The fluid is isotonic with blood plasma, and its composition closely resembles Locke's modification of Ringer's solution. It is clear and colourless, and consists mainly of water (specific gravity, 1,004 to 1,006). It contains the inorganic chemical constituents of the blood plasma, and small quantities of certain organic constituents such as proteins. The amounts of such substances as chlorides, glucose, urea, lactic acid, etc., vary with the level of these substances in the blood plasma, but the correspondence is not absolute, and is altered by disease.

The choroid plexus consists of vascular fringes which project into all the ventricles of the brain. The cerebrospinal fluid is therefore produced in the ventricles and flows into the subarachnoid space through the foramina of Luschka, which are two apertures situated laterally in the roof of the fourth ventricle. The bulk of the fluid flows around the medulla, forward to the base of the brain and over the cerebral hemispheres and returns to the blood through the venous system. Most of the absorption into the blood stream occurs through the arachnoid villi—finger-like processes of the arachnoid which project into the venous sinuses (pacchionian bodies or granulations are large arachnoid villi found only in adults). Some fluid returns by the spinal veins. Cerebrospinal fluid is removed for examination from the dilated parts of the subarachnoid space; two are readily reached from outside the body. One is the prolongation of the space below the end of the spinal cord, which is tapped by *lumbar puncture*; the other is the cisterna magna (cerebello-medullaris) on the posterior aspect of the medulla and under the surface of the cerebellum, which is tapped by *cisternal puncture*. Occasionally fluid is removed from the *lateral ventricles* (see Fig. 2, p. 24).

The changes in the cerebrospinal fluid may affect all or some of its constituents. The *pressure* is abnormal when there is an imbalance between the rate of formation and the rate of absorption. The figures given in the table are for patients in the lateral recumbent position at the beginning of lumbar puncture and before fluid has been allowed to drain away. In the infectious diseases of the nervous system there is a general tendency for pressure to be increased—most marked in cases of meningitis. The total volume of the cerebrospinal fluid is about 100 to 150 c.c., but if allowed to escape 200 c.c. or more may drain away in the twenty-four hours.

The *appearance* of the fluid depends to a large extent upon its cell-content. In *encephalomyelitis* it usually retains its water-like appearance. In *meningitis* there is commonly a departure from the normal, varying from a slightly opalescent

fluid in tuberculous meningitis to a thick, yellow, purulent exudate in the pyogenic forms of meningitis such as meningococcal. Apart from the yellow colour imparted by pus, there is an orange-yellow colour (xanthochromia) which indicates a recent hæmorrhage into the fluid and is only rarely seen in infectious disease. The appearance of a clot, indicating the presence of fibrinogen, is always of pathological significance unless blood has been mixed with the fluid by accident. In tuberculous meningitis, and occasionally in poliomyelitis, the clot forms a delicate web, whereas in purulent meningitis the clot is coarser.

The normal *cells* are mononuclear, usually lymphocytes. In *encephalomyelitis* there is usually a moderate increase in these cells, although in the early stages of *poliomyelitis* polymorphonuclear cells are also present. This also happens in *tuberculous meningitis*. In *purulent meningitis* there is a considerable increase in the number of cells, due to the presence of polymorphonuclear " pus " cells, although, when recovery sets in, mononuclears appear.

The *protein* in the cerebrospinal fluid is small in amount and consists of about equal parts of albumen and globulin. Quantitative tests for protein and qualitative tests for globulin are used. In normal fluid globulin tests are negative. When protein is increased they are positive. Most globulin tests are not true indications of globulin alone because the test material reacts with all proteins.

The *colloidal gold test* is one of a number of tests used to demonstrate an abnormality in the protein content of the fluid. The various results which occur depend upon the total protein and the ratio of albumen to globulin. Fluids with an abnormal protein content cause precipitation of colloidal gold. The degree of precipitation is indicated by the figures 1 to 5, the latter figure indicating complete precipitation. The test is carried out with ten dilutions of the cerebrospinal fluid. The maximum precipitation does not necessarily occur with the least diluted fluid. In *normal* cerebrospinal fluid there is usually no precipitation in any tube, which is indicated thus :—

0000000000

In *abnormal* fluids, if the maximum precipitation occurs in the first three or four tubes, *i.e.*, those least diluted, the result is a *first zone curve*, *e.g.*,

5554321000

This reaction occurs particularly in syphilis, especially dementia paralytica, and in disseminated sclerosis.

If the maximum change is in the middle three tubes the result is a *mid-zone curve, e.g.*,

0123432100

This reaction is of no particular diagnostic significance, but it happens to be common in the encephalitides.

When the maximum change is in the last three tubes, *i.e.*, the most diluted fluid, a *late zone curve* is produced, *e.g.*,

000112333

This type of curve occurs with a higher protein content, especially when the albumen-globulin ratio is also high. It is the type which occurs in purulent meningitis. Colloidal gold reactions have not the diagnostic value that was once attributed to them.

Glucose.—The sugar of the cerebrospinal fluid (glucose or dextrose) follows the level of that in the blood plasma. The figures given in the table are for non-fasting patients.

In patients with acute or subacute meningitis the figure is low, due to the glycolytic (sugar destroying) action of the organism present. In *meningococcal meningitis* the absence of sugar in the fluid is a sign of severity, and its return is a sign of improvement.

Chlorides.—The chloride content of the cerebrospinal fluid follows closely that in the blood plasma. In normal individuals it is a fairly constant figure, so that departures from normal limits are of particular value. In febrile diseases, and where there is vomiting, the concentration of chlorides in the blood and cerebrospinal fluid falls. It is low in the cerebrospinal fluid of meningitis, particularly in *tuberculous meningitis*, in which very low figures (below 600 mg. per 100 c.c.) are not uncommon.

Organisms are present in the cerebrospinal fluid in the purulent meningitides, and in tuberculous meningitis. Pneumococci, streptococci and staphylococci are readily detected. Meningococci may be numerous, few or absent. A purulent fluid in which organisms cannot be found is strongly suggestive of a meningococcal infection. Tubercle bacilli may be difficult to find, and, as their presence is of considerable diagnostic and prognostic importance, prolonged search should be carried out in doubtful cases. The organism may be found in the deposit, or in the clot, or it may be detected only after inoculation of the fluid into a guinea pig. Table XVIII shows that there are no very distinctive differences between the encephalitides and that confusion with tuberculous meningitis is easy, particularly if the tubercle bacillus cannot be detected. The

TABLE XVIII.—CEREBROSPINAL FLUID IN HEALTH AND DISEASE

Disease	Pressure	Appearance	Cells per c.c.	Protein (Mg./100 c.c.)	Sugar (Mg./100 c.c.)	Chlorides (as Na Cl.) (Mg./100 c.c.)	Colloidal Gold
Normal	80 to 160 (children less)	Clear, colourless, like water	1 to 5 lymphocytes	15 to 45 (average 20)	50 to 100	720 to 750 (very constant)	0000000000
Meningism	+ or N (up to 300)	N	N	**Low** or N (5 to 35)	N or +	**Low** or N (620 to 750)	N
Post-infectious encephalomyelitis	+ or N	N	+ or N chiefly lymphocytes (1 to 50)	N or +	N or Sl +	N or Sl low	Variable. Sl changes. N or mid-zone.
Epidemic encephalitis	N or + (up to 200)	N	**+** or N lymphocytes — no polymorphs (1 to 100)	N or +	**N**	**N**	Variable.
Acute poliomyelitis	N or + (up to 300)	N or Sl opalescent ± faint yellow ± delicate clot	**+** to N mainly lymphocytes; some polymorphs, particularly early	N to **+** increases as cells decrease	N or Sl +	N or Sl low	Variable.
Benign lymphocytic meningitis	N or +	N or Sl opalescent	**+** mainly lymphocytes (25 to 1000)	N or +	N	N	Variable. Sl change, usually late zone.
Mumps meningitis	N or +	N or Sl opalescent	**+** mainly lymphocytes (25 to 2000)	N or +	N	N	Variable. Sl change, usually mid-zone.
Tuberculous meningitis	**+**	Opalescent ± faint yellow **Delicate clot**	**+** lymphocytes—some polymorphs	**+**	**Low**	**V. Low** (530 to 680) often below 600	Mid-zone or N (**T.B. +** in deposit or clot).
Purulent meningitis	**+ + +**	**Yellow—opalescent to purulent** Streptococcal — thin, yellow, turbid Meningococcal—thick, yellow, purulent Pneumococcal—thick, greenish, purulent **Coarse clot**	**+ + +** chiefly polymorphs (100 to 20,000)	**+**	**Low**	**Low**	Late or mid-zone. (**Organism +**).

N = normal. Sl = slightly. + = increased (or present if normally absent). The most characteristic findings are in heavier type.

most valuable diagnostic point in such circumstances is the low chloride content.

In *meningism* there is a diluted fluid under pressure. The increase in the water content reduces the relative amounts of protein and chlorides.

The fluid in purulent meningitis presents no difficulty in diagnosis.

Puncture of the subarachnoid space (lumbar and cisternal punctures) is performed for the following reasons :—

1. *Diagnosis* :—
    (*a*) Collection of cerebrospinal fluid. Examination assists in diagnosis and in gauging progress. Estimation of the pressure is also of value.
    (*b*) Introduction of fluids such as lipiodol, opaque to X-rays, to diagnose obstruction by tumour, etc.
2. *Drainage of the Subarachnoid Sac.*—Allowing cerebrospinal fluid to escape to relieve pressure and drain away purulent fluids.
3. *Introduction of Sera and Drugs.*—The intrathecal route is used for administration of therapeutic sera, drugs to produce anæsthesia and drugs for treatment, such as sulphonamide.

CHAPTER XXIV

CEREBROSPINAL FEVER

(*Cerebrospinal Meningitis, Post-basic Meningitis (a variety in children)*)

DEFINITION.—An infection with the meningococcus, which enters through the nasopharynx, invades the blood and localises in the meninges causing an acute purulent inflammation of the meninges of the brain and spinal cord. The clinical picture is variable, but the most characteristic feature is muscular rigidity.

Bacteriology.—The meningococcus (*Neisseria intracellularis, Neisseria meningitidis,* formerly *Diplococcus intracellularis meningitidis* of Weichselbaum) belongs to the genus *Neisseria* (gram-negative cocci) the members of which, with one important exception, the gonococcus, inhabit the nasopharynx. The meningococcus, unlike the other Neisseria of the upper respiratory tract, tends to spread from the nasopharynx into the blood stream. It is a gram-negative coccus which, in the body, is usually found arranged in pairs (diplococci). The adjacent sides of the pair are usually flattened, so that the organism is bean-shaped instead of round. It is difficult to grow except on media enriched with serum or other animal fluids.

The most important fermentation reactions of the three commonest gram-negative cocci are :—

	Glucose	Maltose
N. CATARRHALIS . .	0	0
GONOCOCCUS . .	+	0
MENINGOCOCCUS . .	+	+

By agglutination tests and by absorption of agglutinins meningococci are divided into four types or two groups, but the distinction is not sharp. Intermediate strains and sub-types exist, and there is a certain amount of cross-agglutination

between types. An organism is allocated to a particular type if it produces the maximum agglutination with the corresponding serum. Generally, Type I is responsible for a large percentage of adult cases and Type II for most of the post-basic forms in children. Meningococci contain powerful endotoxins, which are readily released because the organism is easily autolysed, *i.e.*, broken up as the result of the action of a ferment. Considerable importance was attached to endotoxins as they were thought to be responsible for all the toxic features of the disease. Recently exotoxins have been discovered which are believed to contribute to the toxæmia. Not only the organisms themselves but their toxins, both endotoxins and exotoxins, are partly type-specific, *i.e.*, vary slightly in the different strains.

Antisera therefore differ also. Three types are in use :—

1. *Monovalent antibacterial* serum—prepared by injecting horses with one type of meningococcus. This serum is most active against the one type of meningococcus and its endotoxins.

   Type I and Type II sera are available.
2. *Polyvalent antibacterial* serum—prepared by injecting horses with more than one type of meningococcus. It is not so efficient as monovalent serum, but where the type of the organism is unknown, as often happens at the beginning of the illness, polyvalent serum is more likely to be successful.
3. *Polyvalent antitoxic* serum (meningococcal antitoxin)—prepared by injecting horses with exotoxins.

Pathology.—Following infection of the upper respiratory tract (i) the meningococci may be destroyed ; the infection is latent ; (ii) the disease is localised to the upper respiratory tract, causing a rhino-pharyngitis, which sometimes spreads to involve the nasal sinuses, *e.g.*, ethmoid and sphenoid ; (iii) the organism invades the blood stream producing bacteriæmia, but the number of cases in which the disease is limited to bacteriæmia is small ; (iv) but in the vast majority of cases the organisms invade the meninges, thus producing purulent cerebrospinal meningitis.[1]

The membranes involved are the pia mater and the arachnoid. The purulent exudate which collects in the pia-arachnoid mesh (the subarachnoid space) is most marked at the base of

[1] It has been suggested that the organism passes directly from the nose through the cribriform plate to the meninges, or that it travels along lymphatics from infected sinuses to the meninges. The evidence is not convincing.

the brain, over the convexity of the cerebrum, especially in the deeper fissures, and around the big vessels over the cerebellum and down the spinal cord, particularly its posterior aspect. The ventricles are a little distended and contain turbid or purulent fluid. The choroid plexus is swollen and sometimes minute hæmorrhages can be seen. In the most acute cases there is little more than congestion of the membrane and a turbid fluid; in the less acute cases the exudate is thicker and forms a greenish-yellow layer. The brain substance is soft and occasionally foci of necrosis are present adjacent to the ventricles or beneath the pia.

Histologically the vessels are congested and the walls infiltrated with leucocytes; the perivascular lymph sheaths are often filled with lymphocytes. Degenerative changes are present in the lining cells of the membrane, in the epithelium of the choroid plexus, in the superficial cells of the cortex of the brain and sometimes in the nerve roots around which the inflammatory exudate extends. In the pia-arachnoid space the inflammatory exudate consists of a fine network of fibrin enmeshing large numbers of cells, mainly polymorphonuclear leucocytes. Meningococci are often contained without the protoplasm of the polymorphonuclear leucocytes, but may be free in the fluid. The changes in the cerebrospinal fluid are described in Table XVIII, p. 283.

In chronic cases the exudate organises, the membranes are thickened, adhesions form, and the subarachnoid space is occluded in places, particularly about the cerebellum, medulla, and over the cerebral hemispheres. The foramina of Majendie and Luschka, connecting the subarachnoid space with the ventricular system, are obstructed and the flow of cerebrospinal fluid from the ventricles impeded, resulting in *internal hydrocephalus*. The ventricles are distended and the cerebral substance compressed and flattened. If the process is still active the fluid may remain turbid; but activity may cease and the fluid become clear, although hydrocephalus persists.

In other organs there is evidence of toxæmia and of any complications which were present, such as suppurative sinusitis, broncho-pneumonia, suppurative arthritis, etc. Petechial hæmorrhages are commonly present in the skin, serous membranes and suprarenals. If death occurs early in the attack there may be no gross changes in the meninges, but histological examination may show that they are involved.

Incidence.—The disease is rare before three months of age. Although children are most susceptible the disease is not restricted to them, for it affects adolescents and young adults

almost as frequently. One reason for this is that the predisposing factors, which provide opportunity for the transfer of infection, are more operative at these ages and especially among males. Predisposing factors are fatigue, cold and overcrowding. The disease therefore affects young soldiers unaccustomed to rigorous military routine, and sleeping in crowded barracks, especially if they come from rural districts where opportunities for acquiring some measure of immunity are negligible.

The disease occurs *sporadically* in the British Isles, and the post-basic form may be considered endemic in large cities. From time to time outbreaks occur which may assume epidemic proportions. Epidemics are irregular in their behaviour. War conditions are favourable to their spread, particularly among the military population. There is definite *seasonal prevalence*, most cases occurring in winter and spring.

Modes of Spread.—The source of infection is the nasopharynx of infected persons, either carriers or those suffering from the disease. The organism is contained in the droplets and discharges from the upper respiratory tract. Infection of the new host takes place almost invariably by the inhalation of droplets, although occasional transmission by articles freshly soiled by discharges or droplets is still accepted.

Incubation Period.—The incubation period is short in the epidemic form—from **one** to **three** days. Sporadic types usually appear within a week of exposure, *e.g.*, four or five days.

Clinical Features.—The clinical manifestations of the disease are very variable. As already mentioned, the meningococcus may not spread beyond the nasopharynx, or it may invade the blood stream, and not the meninges, or become localised in the meninges as well.

Rhinopharyngitis, although an essential stage of the illness, is usually inconspicuous.

All grades of meningeal involvement are encountered from fulminating cases which prove fatal within a few hours of the onset to chronic post-basic types which may persist for months. In Table XIX the types are classified.

Ordinary Form.—There may be premonitory symptoms for a day or two such as malaise, nausea, anorexia, slight nasopharyngeal catarrh, but usually the onset is abrupt, with severe headache, vomiting, pyrexia, pains in the neck and back and disturbances of the mental faculties. In children a convulsion is not uncommon, and in adults a rigor. The manifestations are those of an irritation of the central nervous system, with evidence of increased intracranial pressure. *Headache* is an early, constant and persistent feature and increases in severity

TABLE XIX

Extent of Invasion by the Meningococcus	Type of Disease Produced	Relative Frequency
Implanted in the nasopharynx	No disease. Latent infection	COMMON.
Rhinopharyngitis	Abortive (" forme fruste ")	Not uncommon during epidemics.
Rhinopharyngitis and bacteriæmia	Septicæmia types : (i) Acute : severe or fulminating (ii) Chronic . . .	 Uncommon Rare.
Rhinopharyngitis, bacteriæmia and meningitis	Acute { Very mild (ambulatory) Acute { Ordinary attacks { Mild, Moderate, Severe } Acute { Fulminating Subacute or chronic In children—post-basic type	Uncommon. COMMON. Rare. Uncommon. COMMON.

as the disease progresses. It is generally diffuse, but may be localised to the occipital or, less frequently, the frontal region. *Pain* may also be experienced in the back of the neck ; it is usually severe but may be excruciating ; movement and coughing make it worse. Mental irritability manifests itself in restlessness, resentment at being examined, sleeplessness during the night (often associated with drowsiness in the day) and delirium ; later irritation gives place to depression and the patient becomes stuporose or comatose. The most characteristic sign is *muscular stiffness*, due to increased tone resulting from irritation of the nervous control of the voluntary muscles. This rigidity is not equally distributed over the body and can be most easily detected in certain situations by the following signs :—

NUCHAL RIGIDITY is constantly present. In normal people the neck can be readily flexed so that the chin touches the front

of the chest. In meningitis the stiffness of the muscles of the back of the neck interferes with this movement. On trying to flex the head with the hand of the examiner under the occiput: (i) abnormal resistance is encountered; (ii) pain is produced; (iii) flexion is either considerably diminished or impossible; (iv) in more severe cases, where the back is stiff and straight (*orthotonos*), the poker-like rigidity may permit the patient's back to be lifted off the bed without the neck flexing.

HEAD RETRACTION AND OPISTHOTONOS.—Later on the contracted muscles of the back of the neck bend the head backwards (*head retraction*); and an extension of the process to the muscles of the back of the trunk causes arching backwards of the whole body (*opisthotonos*). These signs are not nearly so constant as neck rigidity and are more likely to occur in prolonged cases, particularly in post-basic types.

KERNIG'S SIGN is most valuable and is nearly always present. It depends upon the stiffness of the muscles of the back of the thigh. The patient should be lying on his back with both lower limbs flat on the bed. The test is performed by attempting to extend one leg at the knee joint, whilst the thigh is flexed on the abdomen. The limb which is to be tested is flexed at the hip joint to a right angle, so that the thigh is maintained in the perpendicular position during the test. The leg is then extended at the knee joint. When limitation of extension is elicited, Kernig's sign is *positive.*

BRUDZINSKI'S SIGNS are not very constant, and are probably in the nature of reflexes. The *neck* sign is positive if, on flexing the head of the supine patient, the thighs and knees flex at the same time; it is usually painful to the patient with meningitis. The *leg* sign (*contra lateral reflex*) is positive if, on flexing one lower limb upon the abdomen, the opposite limb flexes simultaneously.

Other muscular phenomena occasionally seen are muscular twitchings or tremors and weakness (paresis), which may affect the face, muscles of the eyes or limbs.

Ocular symptoms of some sort are common but not constant. The pupils are usually dilated and react sluggishly to light. Strabismus sometimes occurs, but nystagmus, ptosis and optic neuritis are less common. Apart from the nervous lesions, conjunctivitis and other local ocular complications of the infection occur, and are considered later.

The abdominal reflexes are usually absent; the deep jerks are often exaggerated in the early stages, but soon become depressed or lost; the plantar reflexes are sometimes extensor (*Babinski's sign*). Differences on the two sides are not un-

common. *Retention of urine* and constipation are uncommon and may be followed by *incontinence.*

With increase in intracranial pressure the usual manifestations appear : severe headache, vomiting of the cerebral type (effortless and unrelated to food), optic neuritis (papillœdema), convulsions, slow pulse and Cheyne-Stokes' respiration. These are all serious signs.

Cerebrospinal fever, being essentially a bacteriæmia, is always associated with general as distinct from nervous symptoms. Pyrexia is usually irregular and is moderate or marked (102° to 105° F.). The pulse rises with the temperature, except when the increased intracranial tension causes it to be relatively or absolutely slow. Alterations in the rate rhythm and depth of respiration are usually bad prognostic signs. A rise in rate may indicate pulmonary complications such as broncho-pneumonia. Cheyne-Stokes' respiration is evidence of serious intracranial pressure.

Anorexia and loss of weight are common, and wasting may become extreme in the protracted cases.

Rashes sometimes occur, but their frequency varies in different epidemics. Generally, the presence of a rash is evidence of severity. Erythematous rashes (sometimes scarlatiniform, sometimes mottled and morbilliform, but not uniformly distributed) are toxic in origin. *Hæmorrhagic* eruptions are due to bacteriæmia, the meningococcus being recoverable from the lesions. These appear early on the first or second day and may take the form of a few scattered petechiæ, or, in the worst cases, widespread ecchymoses. These cutaneous hæmorrhages are responsible for the synonym "spotted fever."

Herpes febrilis sometimes occurs towards the end of the first week, and is due to a specific virus activated by the disease.

Recrudescences and relapses are not uncommon. The former occur early, a few days after the patient has shown definite signs of improvement ; the latter appear in convalescence.

Complications and sequelæ are more likely to occur in protracted cases, but with modern methods of treatment they are now less common. Some are due to direct spread of infection from the nasopharynx ; some are the result of the damage to the nervous system ; others to extra-meningeal localisation of the organism from the blood stream.

Acute suppurative sinusitis involving most commonly the ethmoids or sphenoids is the result of direct extension from the nasopharynx. The infection may persist in the nasopharynx and sinuses in *convalescent carriers.* Direct involvement of the middle ear (*otitis media*) also occurs, but like *broncho-pneumonia,*

which is common in fatal cases, it is frequently due to a secondary hæmolytic streptococcal infection.

Various *ocular* complications occur. The inflammatory exudate around the optic nerve may result in permanent *blindness*. *Conjunctivitis* at the beginning of the illness is usually transient and insignificant. Later it may recur and herald the onset of *keratitis, corneal ulceration* and *hypopion iridochoroiditis* and *panophthalmitis*. These are usually unilateral and are not common ; are probably infections from the blood stream rather than direct spread from the nose ; and may produce blindness from local damage as distinct from that of central origin.

The *auditory nerve* may be involved in the intracranial inflammatory process. Subjective symptoms may occur and partial or complete *nerve deafness* may follow. In young children complete deafness may result in mutism. A sequela is noises in the head.

Chronic hydrocephalus results from the interference with the normal circulation of cerebrospinal fluid due either to obstruction at the foramina or to permanent damage to the meninges diminishing the area of absorption. It is usually associated with some degree of *mental impairment*, which, however, may occur apart from hydrocephalus.

The disease may give rise to inflammation of serous linings other than the meninges, the organism being deposited from the blood stream. *Multiple arthritis* may occur early, particularly in hæmorrhagic cases ; *monarticular suppurative arthritis, e.g.*, in the knee joint, occurs later in the disease but rarely produces permanent damage. *Pericarditis* is not common and not necessarily fatal ; *endocarditis* is rare. *Pleurisy* sometimes occurs.

Complications may occur in the extrameningeal types.

Permanent damage, apart from deafness, is rare in cases adequately treated. Mild sequelæ such as headache, noises in the ear, temporary disturbance of gait and squint may improve in the course of time.

Post-basic meningitis is a form of meningococcal meningitis which occurs endemically in children under one year of age. There is no essential difference between it and the ordinary form of the disease. The differences in clinical manifestations are due to two factors—the subacute nature of the disease and the age of the patient. In Great Britain post-basic meningitis is usually due to a Type II meningococcus, and this may be one of the factors responsible for the chronicity of the disease.

The attack may begin suddenly with convulsions, vomiting and gastro-intestinal disturbances, or insidiously, with drowsiness and occasional vomiting. For the first few days the nature of the disease may be readily overlooked. Signs of muscular rigidity are not so constantly present. Neck rigidity and Kernig's sign may be doubtful or absent. The infant is fretful, resents examination, cries out from time to time, and may exhibit some retraction of the head. Gradually the clinical features of the disease become more apparent. The illness runs a protracted course, with irregular pyrexia, usually of moderate degree. Anorexia is marked, the patient becomes semi-conscious, nourishment is difficult to administer and the infant becomes thin. Head retraction and opisthotonos are marked. The arching of the back may become so pronounced that the occiput and heels may almost touch. The increased intracranial tension causes bulging of the anterior fontanelle. Blindness, without optic neuritis, is frequent, but deafness is rare. Strasbismus is occasionally seen early in the disease, when it may be a useful diagnostic sign. Recrudescence of symptoms and relapses commonly interrupt the stage of recovery. The illness may persist for weeks or months. The prognosis until recently was poor; a high percentage died, and among those that recovered, sequelæ such as blindness, hydrocephalus, and mental deficiency were common, but treatment with sulphonamides has improved the outlook considerably. Post-basic meningitis is not the only form which occurs in infants: the acute type is met with particularly during epidemics.

Fulminating types are characterised by the abruptness of onset and the rapidly fatal course. Death takes place within two days, and may occur as quickly as five hours after the onset.

Two forms are described, bacteriæmic (see septicæmic types) and the meningeal. The distinction is not important, for in both the seriousness of the disease depends upon an overwhelming general infection.

The symptoms at the onset are variable. There may be sudden severe headache, vomiting, diarrhœa, pyrexia and collapse; or the patient may suddenly become maniacal or unconscious without premonitory symptoms. Hæmorrhages into the skin are common. If the meninges are not involved the cerebrospinal fluid is normal. If they are, the fluid may be clear or slightly turbid and contain relatively few cells—mostly lymphocytes—indicating an early stage of the disease with little reaction by the phagocytic cells. Meningococci are

present in variable numbers. In all cases coma and death rapidly supervene.

Septicæmic Forms.—The distinctive feature of this unusual type is the escape of the meninges. Most cases are severe or fulminating and the absence of nervous involvement is due to the fact that death supervenes before localisation occurs; less severe types are seen in which this is not the reason. Since bacteriæmia occurs in every case of cerebrospinal fever there are no characteristic clinical features; but cutaneous hæmorrhages are prominent. Headache, shivering, vomiting and persistent pyrexia are usual. A low grade or chronic type of septicæmia sometimes occurs which may persist for months if untreated. In these septicæmic types localisation sometimes takes place in serous cavities other than the meninges.

Chronic Forms.—*Ordinary* cases of cerebrospinal meningitis sometimes become *chronic*, especially in the absence of specific treatment. Irregular pyrexia, meningococcal symptoms and abnormality of the cerebrospinal fluid persist for months. The mental faculties deteriorate, incontinence of urine and fæces occurs, the patient becomes emaciated and bedsores and septic complications supervene. Death takes place after a few months from hydrocephalus or intercurrent infection.

Post-basic meningitis—the commonest chronic form of the disease—and the rare chronic septicæmic type have already been described.

Case Fatality.—Wide variations occur, influenced by such factors as age, type of the disease, differing virulence of the prevalent organism (generally epidemic cases are more fatal than sporadic ones) and the uncertain response to treatment. The disease is most fatal in children under one year of age. Rates as high as 70 per cent. have occurred but are now much lower. Prognosis improves with age, until twenty years, and then worsens.

At favourable ages, and with successful treatment, the case fatality may be as low as 5 to 10 per cent.

Laboratory Aids to Diagnosis.—Two investigations are always employed because a diagnosis can only be made with certainty if one or both are positive. They are (i) search for the meningococcus, (ii) examination of the cerebrospinal fluid.

The meningococcus is present in the *nasopharynx* at the beginning of the illness, and usually, but by no means always, disappears in a few days. The organisms may persist for weeks or months, the patient becoming a *convalescent carrier*. A negative finding therefore possesses little diagnostic significance. Because of the rapidity of disappearance and the

difficulty of bacteriological differentiation, swabbing of the nasopharynx is not used as a routine for *diagnosis*, but is used for *release cultures*.

Although meningococci are present in the *blood stream* in the early stages they are sparse and difficult to cultivate. Thus while no significance can be attached to a negative result, a positive one is conclusive. Routine blood cultures should therefore be carried out.

In the *cerebrospinal fluid* the organisms can be found on direct smear in a high percentage of cases. Furthermore, cytological, biochemical and immunological changes may furnish positive evidence. The fluid is centrifugalised, the deposit is examined by direct smear and culture and the supernatant fluid is tested for specific antigens (precipitinogens). The changes are listed in Table XVIII. Most importance is attached to the presence of a turbid or purulent fluid under pressure, containing large numbers of pus cells, mainly polymorphonuclears, and the presence of meningococci. The organisms are either free in the fluid or lying within the cytoplasm of the pus cells. They may be present in large numbers or may be so few that prolonged search is necessary. The cerebrospinal fluid should always be cultured. If there is any discrepancy between the direct smear and the culture, the former is positive and usually the latter negative because of the difficulty of cultivation. When the meningococcus is isolated it should be typed, so that if a type specific serum is available it can be used in treatment.

The meningococcus disintegrates easily and the cerebrospinal fluid contains antigens released from the organism. If the supernatant fluid is added to antimeningococcal precipitating serum, an opaque ring forms at the junction. By using type specific serum it is sometimes possible to type the organism without awaiting the isolation of the meningococcus.

Differential Diagnosis.—I. INTRACRANIAL DISEASES.—(*a*) Other types of meningitis. (*b*) Encephalomyelitis such as acute poliomyelitis and encephalitis lethargica and post-infective forms. (*c*) Meningism. (*d*) Miscellaneous.

II. CONDITIONS WITHOUT INTRACRANIAL DISEASE.—In children the usual mistake is to diagnose meningitis when none exists ; but the more serious mistake of overlooking meningitis is not uncommon, particularly if the onset is insidious. Once the nervous system is suspected the diagnosis is practically certain, for examination of the cerebrospinal fluid (which should be carried out immediately such a suspicion arises) either

confirms the diagnosis or permits differentiation of most of the intracranial conditions likely to be mistaken for cerebrospinal fever. Nevertheless, the clinical differences often permit differentiation before lumbar puncture is performed.

In *other purulent meningitides* a focus of disease may be discovered elsewhere and indicate the nature of the infection, but ultimate differentiation depends upon the detection of the causative organism in the cerebrospinal fluid. The naked-eye appearance of the fluid may be suggestive: meningococcal infections tend to produce a thick opaque yellow fluid; streptococcal, a thin yellow turbid fluid; pneumococcal, a thick greenish one.

1. STREPTOCOCCAL MENINGITIS is usually otogenic, the sequel of otitis media, mastoiditis or its extensions (*vide* Chapter VI). As aural conditions and their complications require immediate surgical intervention, it is important to exclude them in every case of meningitis by *an examination of the drumhead.*

Sinusitis, nasal operations, fracture of the skull, erysipelas, and other facial infections are occasionally complicated by streptococcal meningitis. In scarlet fever the condition is usually otogenic, rarely a metastasis following septicæmia.

2. PNEUMOCOCCAL MENINGITIS is of septicæmic origin and is frequently associated with lobar pneumonia. Cortical involvement is a prominent feature; muscular spasms and tremors are common; head retraction and opisthotonos are not marked.

Staphylococci, influenza bacilli, typhoid bacilli, colon bacilli, and other pyogenic organisms occasionally cause a purulent meningitis.

3. TUBERCULOUS MENINGITIS is secondary to a focus elsewhere which in children especially may be occult. It is usually preceded by a variable period of ill-health—seldom less than a week—the result of dissemination of tubercle bacilli in the blood stream. The chief differences between *typical* cases of meningococcal and tuberculous meningitis are tabulated in Table XX.

4. ASEPTIC MENINGEAL REACTION (*acute serous meningitis, meningitis sympathica*) may resemble purulent meningitis very closely. It is generally accepted as an inflammatory reaction of the meninges due to an adjacent septic focus, but without bacterial invasion. The

TABLE XX

	Meningococcal	Tuberculous
Previous health .	Healthy	Unhealthy.
Onset . .	Sudden	Insidious.
Early convulsions	Not so common	More common.
Evolution . .	Rapid	Slow and irregular.
Pyrexia . .	Usually high	Often slight.
Prostration .	Considerable	Not so pronounced.
Muscular rigidity, *e.g.*, nuchal	Definite and constant	Not so striking or so constant.
Head retraction .	Frequent	Not so frequent.
Opisthotonos .	Not uncommon	Practically never occurs.
Ocular palsies .	Occasionally seen	More common.
Fundus . .	Sometimes optic neuritis	Sometimes choroid tubercles (late).
Cerebrospinal fluid	Purulent Pus cells Meningococci	Clear or opalescent. Lymphocytes. Low chlorides. Tubercle bacilli.
Age incidence .	Not uncommon in children under one year	Rare in children under one year.

commonest causes are extradural abscess or venous sinus thrombosis due to mastoid or nasal sinus infection. The septic focus must be removed lest the organisms invade the cerebrospinal fluid or brain. The fluid is cloudy or even purulent and under increased pressure. There is a variable degree of increase of cells, chiefly polymorphonuclear leucocytes. The distinguishing features are the normal sugar content and the absence of organisms. After removal of the septic focus the fluid returns to normal.

5. BENIGN LYMPHOCYTIC MENINGITIS (*acute lymphocytic choriomeningitis, acute aseptic meningitis*).—A rare disease due to a specific filterable virus which affects man and animals. Its particular features are the benign course, absence of complications, and complete recovery which occurs in usually ten to fourteen days, but may be delayed for five or six weeks. The cerebrospinal fluid is clear or slightly opalescent and shows a lymphocytic pleocytosis of 50 to 1,000 per c.mm. Polymorphonuclear leucocytes are *not* present. Protein is normal or slightly increased; sugar and chlorides are normal; and cultures are sterile. The colloidal gold test is usually of the late zone type. Treatment consists in repeated lumbar puncture and general nursing measures.

6. MENINGISMUS is never primary, but occurs in the course of other infectious diseases, usually at the onset. It is most commonly seen in children with pneumonia, influenza and typhoid fever.

At the onset of acute febrile illness there is a fall in the blood chloride. Osmotic pressure is lowered and the serum becomes hypotonic, resulting in increased filtration or production of cerebrospinal fluid and consequent increase in pressure. The clear fluid has a low *chloride* and low *protein* content which, however, may still be within the lower limits of the normal; thus, apart from increase in pressure, the cerebrospinal fluid will be "normal."

The syndrome may closely simulate meningitis with head retraction, nuchal rigidity and other meningeal signs. When this occurs during acute toxæmia and delirium, *e.g.*, in lobar pneumonia and typhoid fever, where signs in other systems may be difficult to detect, the only means of differentiation is the examination of the cerebrospinal fluid. Lumbar puncture, by reducing pressure, usually alleviates the symptoms. The condition is particularly common with the apical type of lobar pneumonia.

7. ACUTE POLIOMYELITIS occurs in warm weather, whereas meningococcal meningitis is most prevalent in winter and spring; but sporadic cases may occur at any time. The stage of poliomyelitis which may be mistaken for meningitis is the early "meningeal" phase. It is usually of short duration, meningeal signs are seldom marked, hyperæsthesia is common and febrile herpes rare. Flaccid paralyses, usually of the limbs, soon appear and meningeal signs then abate. In meningococcal meningitis meningeal signs are persistent, hyperæsthesia is much less prominent, *herpes febrilis* is common, and paralyses, if they occur, are late and rarely extensive. Lumbar puncture immediately differentiates the two conditions (*vide* Table XVIII, Chapter XXIII). Repeated convulsions, indicative of cortical irritation, are more suggestive of polioencephalitis.

8. POST-INFECTIVE ENCEPHALOMYELITIS is a complication of several infectious diseases, of which the commonest are measles (*q.v.*), vaccinia (*q.v.*), smallpox (*q.v.*) and influenza.

The histo-pathological changes are essentially the same whatever the primary disease. There is a diffuse perivascular demyelination which is more suggestive of a toxic process than an infective one.

The cerebral symptoms appear while the characteristic signs of the primary disease are still present, or a few days

after these have subsided. The recent existence of such an infectious disease suggests the cause of the cerebral condition. At first there is evidence of a more or less diffuse involvement of the nervous system. As the condition evolves the diffuse features are replaced by localised manifestations in one or more parts of the nervous system. Depending upon the site of these local exacerbations, various types of the disease occur—*meningitic*, *encephalitic*, *myelitic*, *multiple cerebral foci*, *mental*, *hemiplegic*, *aphasic*, *paraplegic*, *cerebellar* or *ataxic*. The initial symptoms vary from slight apathy or irritability to profound stupor or delirium. Convulsions are common and general muscular rigidity is frequent. The patient may die at this stage, or, if recovery occurs, consciousness returns and the localised manifestations appear. Sometimes the preliminary period of diffuse manifestations is absent, and the localised lesion is present from the onset. The changes in the cerebrospinal fluid are variable; the most common finding is given in Table XVIII.

9. *Subarachnoid Hæmorrhage* may resemble meningitis, but the onset is different. It results from rupture of a pial vessel due to disease or trauma. In the spontaneous type the onset is dramatic, with signs of sudden meningeal and root irritation. The patient is seized with violent pains in the head and back. He may fall unconscious for a time or be seized with giddiness and vomiting.

The sudden onset with rigid spine and limbs, pain in the head and absence of coma constitute a suggestive syndrome. Sometimes pathognomonic retinal hæmorrhages are present. The diagnosis is confirmed by finding blood in the cerebrospinal fluid.

10. DISEASES WITHOUT INVOLVEMENT OF THE MENINGES.—Almost any acute febrile illness at the onset may be mistaken for meningitis, particularly if headache is a prominent symptom; if the toxic state is marked by delirium; if it starts with a convulsion; if meningismus is present; or if hæmorrhages into the skin occur. In meningitis the nervous manifestations persist, whereas those which occur at the onset of febrile illnesses tend to pass off as the characteristic features of the disease appear.

In *scarlet fever* the appearance of the throat and the rash differentiate the condition. In *influenza* differentiation may be difficult at the onset. *Pneumococcal infections* may be confused with meningitis because of the toxæmia and delirium, or because of meningismus, or because there is actually a pneumococcal infection of the meninges. In lobar pneumonia the rapid

respirations suggest the diagnosis. In both *typhus fever* and *toxic smallpox* the sudden illness, toxæmia, and purpuric prodromal rash are causes of confusion. In typhus the Weil-Felix reaction is positive, and in both typhus and smallpox the cerebrospinal fluid is normal. *Acute abdominal conditions* sometimes require differentiation from these fulminating cases. *Typhoid fever* is also mistaken for meningitis. The recovery of the causal organism from the blood or stools, the positive Widal reaction, and the normal cerebrospinal fluid distinguish it. *Infections of the ear* which may cause confusion are (i) simple otitis media; (ii) local complications such as mastoiditis, venous thrombosis, with or without an aseptic meningeal reaction; (iii) petrositis with localised meningitis, causing Gradenigo's syndrome, *i.e.*, associated with paralysis of the ipselateral external rectus muscle of the eye, causing a squint; (iv) actual septic meningitis. In infants the intoxication of *acute gastro-enteritis* may produce symptoms suggestive of meningitis, but with the former the fontanelle is *depressed* as the result of the dehydration, whereas in the latter it is *bulging* from increased pressure of the cerebrospinal fluid.

In the chronic septicæmic type of meningococcal infection differentiation from other prolonged septicæmic or toxic states is necessary, *e.g.*, rheumatic fever, malaria, typhoid, subacute bacterial endocarditis, miliary tuberculosis, brucellosis and other septic diseases.

Treatment.—Administration of specific serum and of sulphonamides, drainage of the subarachnoid space and proper nursing are the essential lines of treatment, and the earlier they are instituted the better the prognosis; *there must be no delay.* Lumbar puncture must be performed and the cerebrospinal fluid examined immediately. If the fluid is turbid or purulent, specific treatment must be given at once in anticipation of a positive finding. Blood culture is also essential.

1. SERUM.—Unless the type of meningococcus is known, *polyvalent* serum should be injected intravenously at the time of blood collection for culture. If the type is known, a type-specific serum, if available, should be used. If an adequate initial intravenous dose is given and the response is satisfactory, no further serum is necessary. The dose of concentrated serum should be 30 c.c. for children and 60 c.c. for adults, diluted with twice its volume of 10 per cent. glucose in saline.

The injection should be made slowly, *by gravity at body temperature*, and with caution. Adrenalin should be at hand in case the patient develops symptoms of serum shock (see

p. 25. It may be necessary to venesect in order to introduce the serum.

Practical difficulties with intravenous administrations frequently arise, and it may not be possible to give all the serum, or any of it, by this route. In such circumstances the intrathecal, intramuscular or intraperitoneal route may be used, the serum being given undiluted but warm. Formerly the *intrathecal route* was invariably employed, as it was thought that the antibodies of the serum were thereby brought into direct contact with the organism and its endotoxins, but greater importance is now attached to the general infection and toxæmia. Moreover, serum injected intrathecally tends to irritate the inflamed meninges, and "aseptic meningitis" may be set up which increases the meningitic symptoms of the disease. If the intrathecal route is used, cerebrospinal fluid must first be allowed to escape, and the amount of serum injected must be less in volume than the fluid withdrawn, otherwise the increased intrathecal pressure is aggravated. Serum administered intravenously reaches the cerebrospinal fluid, but only in small amounts.

It is sometimes necessary to give a second dose of serum, but rarely a third. If the patient fails to respond to the first or second injection, another product may be tried as it may contain more specific antibodies.

2. SULPHONAMIDES such as sulphanilamide and sulphapyridine have revolutionised the treatment of meningococcal infections, and must never be withheld whether serum is given or not. Administered by mouth they are rapidly absorbed from the alimentary canal and are present in the cerebrospinal fluid in concentrations almost as great as in the blood. The dosage required is that stated in Chapter X, p. 83, for severe bacterial infections. Other routes, such as the intramuscular and intrathecal, have been tried, but are less effective and should be reserved for the patients unable to take by mouth. If the patient is semiconscious, administration by nasal or stomach tube may be tried. Benzyl-sulphanilamide does not reach the cerebrospinal fluid and therefore is unsuitable in this disease.

3. DRAINAGE is undertaken firstly to relieve pressure, and secondly to conform with the general surgical principle that a purulent exudate under pressure should be drained. It is effected by *daily lumbar puncture* of the subarachnoid space. The pressure should be taken with a manometer, and fluid allowed to escape until a pressure of 70 or 80 mm. is reached, or until the rate of flow from an ordinary lumbar puncture

needle (size 16 standard millimetre gauge) is about 10 drops per minute. An anæsthetic is not essential, except in restless and difficult patients, for whom a general or basal anæsthetic may be required. In adults a local anæsthetic may suffice. Sometimes "dry-puncture" is encountered—no fluid escaping. This may be due to the thickness of the fluid or to adhesions in the subarachnoid space causing loculation. The commonest cause is incorrect technique—failing to enter the subarachnoid space. When the lumbar route is unsatisfactory, *cisternal puncture* can be performed. The technique is simple, but there are dangers because of the proximity of important structures. The most common mishap is damage to a blood vessel, causing cisternal hæmorrhage.

When there is evidence of internal hydrocephalus—usually late in the disease—*ventricular puncture* can be used. In infants it is performed by entering the needle through one of the lateral angles of the anterior fontanelle and tapping the lateral ventricle. In older patients a hole must be bored through the skull.

Instead of *intermittent* drainage, as described above, *continuous* drainage, usually by the lumbar route, is sometimes performed. Technical difficulties, particularly in children, prevent its routine use.

4. GENERAL MANAGEMENT is important. All external sensory stimuli should be avoided. The patient should be put to bed in a quiet, shaded, warm, well-ventilated room. The position should be changed frequently to avoid bedsores and hypostatic congestion of the lungs. The recumbent position is usually the most comfortable. If opisthotonos is present, a pillow under the back provides support. The skin, particularly at pressure points, and the mucous membranes of the mouth, nose and eyes require frequent attention. The usual fever diet should be given (see p. 86). If the patient is semiconscious, nasal feeding or rectal salines and glucose should be employed. The bladder and bowels should be watched, and retention of urine and constipation treated on the usual lines. If the patient is incontinent, bed-linen should be changed as soon as soiled and the back and skin protected, otherwise bed-sores are likely. The chart should be carefully watched: the *temperature* for the progress of the infection, the *pulse* for evidence of increased intracranial tension and the *respiratory rate* for signs of pulmonary complications. Restlessness is to be treated by sedatives, or an ice-bag to the head, or by lumbar puncture.

Estimation of Progress and Prognosis.—Successful response to treatment may be rapid or gradual. In the most favourable

cases amelioration of symptoms and signs may appear in twenty-four to forty-eight hours ; in others definite improvement cannot be detected for a week. In a few cases no apparent effect is to be noted ; the disease pursues the course of an untreated case, either improving slowly or, more commonly, deteriorating and dying.

Progress and prognosis are gauged by the clinical manifestations and the character of the cerebrospinal fluid. Good prognostic signs at the beginning of the illness are a relatively high percentage of *intracellular* meningococci, indicating active phagocytosis, or absence of organisms, indicating that they have been rapidly destroyed. Delirium, coma and cutaneous hæmorrhages, a xanthochromic (yellow-coloured) fluid, and large numbers of *extra cellular* meningococci are of unfavourable import. Signs of improvement are decline in pyrexia, subsidence of toxæmia, abatement of delirium, restlessness or drowsiness, return of mental faculties to normal, and improvement in the appetite. The meningeal signs usually disappear more slowly, and the cerebrospinal fluid often provides earlier evidence of change.

The following changes in the fluid are of good omen :—

(i) Rapid disappearance of organisms.

(ii) A change in the predominant type of cell from polymorphonuclear to mononuclear.

(iii) An improvement in the appearance of the fluid from purulent to turbid and ultimately to clear, with a corresponding decline in the number of cells. This process is usually slow, but, if progressive, is a valuable sign. The fluid may become clear while as many as 100 cells per cubic centimetre are still present. If serum is being given intrathecally, improvement in appearance may be obscured by a cellular reaction due to its irritating effect.

(iv) Rapid return of sugar.

Unfavourable signs are the reverse of the above, particularly the persistence of organisms or their return after a temporary period of absence.

SUMMARY OF CHAPTER XXIV

Stages : Nasopharyngitis, bacteriæmia, purulent meningitis.

Chief Signs : Muscular rigidity—neck rigidity, Kernig's sign, head retraction. C.S.F.—pus cells and meningococci, intracellular and extracellular.

Treatment : Serum, sulphonamide, drainage and nursing.

CHAPTER XXV

ACUTE POLIOMYELITIS AND POLIOENCEPHALITIS

DEFINITION.—An acute infection with a filterable virus which characteristically, but not invariably, affects the central nervous system, with particular affinity for the grey matter of the anterior horns of the spinal cord. The typical clinical manifestations are fever and flaccid paralysis. The tendency is for the original extensive paralysis to clear up spontaneously, except for residual paralysis in certain groups of muscles, which remain permanently paralysed and atrophy rapidly.

Incidence.—Acute poliomyelitis occurs mainly, but not exclusively, in children. The vast majority of patients are under five years of age, but during epidemics older children and adolescents are frequently affected. Infants born of immune mothers are believed to retain their infantile immunity until one year of age. The disease is widespread throughout temperate zones and occurs both endemically and epidemically. In cities a constant latent immunisation of the population is going on, so that when a virulent strain is prevalent the chances of an epidemic spread are not so great as they are in a rural community. The disease is apparently becoming more prevalent in the United States, where serious epidemics have occurred, even in the big cities.

Pathology.—The filterable virus which is responsible has been extensively studied experimentally in monkeys. In patients suffering from the disease it has been found in the nasopharynx, the fæces and the central nervous system, but not in the circulation or other viscera. Two theories are held concerning its spread in the body :—

(i) The most widely accepted view is that the disease is primarily and essentially an infection of the nervous system, because the virus can affect only nervous tissue, *i.e.*, is strictly neurotropic. According to this view the virus is deposited in the nose and travels along the olfactory nerves to the brain and spinal cord. The path traversed has been worked out in detail. The virus invades the olfactory hairs—the terminal processes of the olfactory nerves—spreads along the

axis cylinders of the nerves to the olfactory bulbs and tracts, thence by various tracts to the brain, medulla and spinal cord, where it particularly affects the *anterior horn cells.*

(ii) The alternative hypothesis is that the virus invades the blood stream and localises in the central nervous system, where it exerts its selective action. The portal of entry may be the nasopharynx or the alimentary canal.

In whichever manner invasion occurs, by the time paralysis appears the virus is present throughout the central nervous system. At autopsy, changes are found in the nervous system, reticulo-endothelial system, lymphatic system and intestinal tract. The naked eye changes in the nervous system are not marked or characteristic. Congestion and œdema, particularly of the cord and brain stem, and slight engorgement of the vessels of the meninges are the usual findings. Occasionally small hæmorrhages into the substance of the brain and cord are seen. On section of the cord, the substance mushrooms over the cut edges of the meninges—evidence of the tension of the swollen cord inside the fairly rigid membranes. Sometimes gross changes in the grey matter of the cord—areas of softening and hæmorrhage—can be seen. Microscopically these are :—

(i) *Vascular changes :* congestion, œdema, perivascular infiltration or cuffing with lymphocytes, and hæmorrhages.

(ii) *Nerve cell changes :* degeneration of cells, particularly motor cells of the anterior horns.

(iii) *Glial cell changes :* infiltration of the interstitial tissue by cells which remove the dead cells by phagocytosis and repair by gliosis, the form of fibrosis which occurs in the nervous system.

These changes are found chiefly from the mid-brain downwards and are most marked in the lumbar and, to a certain extent, in the cervical cord. Changes, however, may be detected throughout the nervous system, including the meninges and nerve roots.

The reticulo-endothelial and lymphatic systems show hyperplasia throughout the body, resembling a mild degree of status thymicolymphaticus. In the alimentary tract this takes the form of enlargement of the lymphoid tissues of the lower ileum and cæcum, including Peyer's patches. Hæmorrhages into the mucosa of the stomach are common. The

tonsils and thymus are enlarged. Changes in the lungs depend upon respiratory failure ; small areas of collapse and emphysema are sometimes found. Secondary broncho-pneumonia also occurs.

Modes of Transmission.—It is generally accepted that the disease is conveyed by droplets expelled from the nose of carriers and cases. *Infection* spreads widely among the population, but the percentage of persons who develop the *disease* is small. Actual case to case spread is therefore not common and considerable importance is attached to the intermediate carrier. The virus usually enters the new host by the inhalation of infected droplets, although infection by the ingestion of contaminated milk is still believed to occur.

Incubation Period.—This is uncertain ; it is commonly given as **seven** to **fourteen** days, with limits of five to twenty-one days.

CLINICAL FEATURES

The characteristic clinical feature of poliomyelitis is a flaccid paralysis of the muscles ; but the stage in which this occurs constitutes only one phase of the disease and is not constant. Nevertheless, it is convenient to divide the disease into (*a*) the *preparalytic* stage, (*b*) the *paralytic* stage.

Signs suggesting a diffuse invasion of the central nervous system sometimes occur in the preparalytic stage, so that diagnosis may be possible before paralysis appears. Initial constitutional symptoms and local manifestations in the respiratory and intestinal tracts sometimes precede nervous manifestations. It is possible then to re-divide the clinical course of the disease into (i) the initial systemic phase and (ii) the nervous phase (*vide* Schema, Table XXI).

SYMPTOMS are :—

(i) *Respiratory :* coryza, sore throat or cough.
(ii) *Gastro-intestinal :* vomiting, diarrhœa or constipation.
(iii) *General :* pyrexia, headache, drowsiness, restlessness and irritability and sweating.

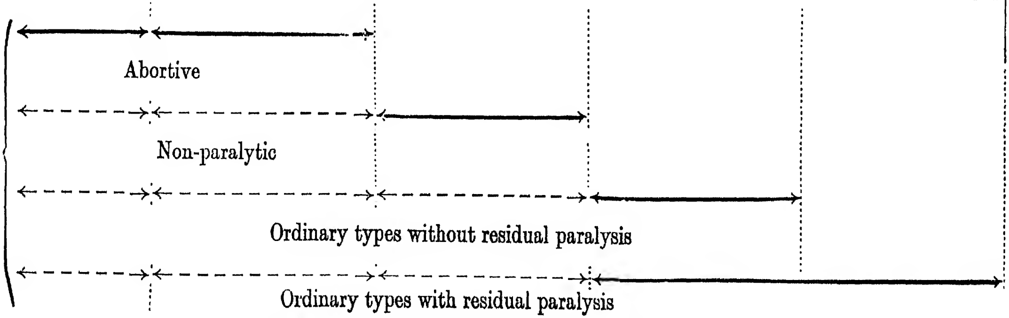
The onset is usually acute, but the initial manifestations are seldom severe. In many cases only one or two of the above symptoms are present. Pyrexia (99° to 103° F.) and headache are most constant. If constitutional symptoms are marked they may focus attention and, in the case of a child in bed, the onset of paralysis may be overlooked. At this stage objective signs may be absent and an early diagnosis can only

TABLE XXI

POLIOMYELITIS : Stages and Types

Invasion	Pre-C.N.S. Invasion. INITIAL SYSTEMIC PHASE.			C.N.S. Invasion. NERVOUS PHASE.		Recession. Recovery.
Symptoms	At portal of entry	General disturbance	Latent	Of diffuse involvement of C.N.S.	Of selective action on anterior horn cells and elsewhere	Permanent paralysis.
Stages	PREPARALYTIC				PARALYTIC	SEQUELÆ.

Types



(Broken lines within arrowheads indicate stages which may be absent)

be inferred in the presence of an epidemic. Not infrequently the disease *aborts* after the initial stage, and in such cases the suspected diagnosis of poliomyelitis can never be confirmed. On the other hand, *no* initial symptom may precede the nervous phase.

LATENT PERIODS.—A latent period may follow the initial stage and last from a few hours to a few days. The patient may feel well, or he may complain of malaise. The temperature is usually normal. This latent period divides the pyrexial phase of the disease into two—the first " hump " due to the initial symptoms and the second " hump " to the nervous symptoms, hence the so-called " dromedary " chart.

NERVOUS PHASE.—When the nervous phase begins, there is evidence of diffuse involvement of the whole nervous system—a *meningo-encephalomyelitis*. Not infrequently the meningeal and sensory manifestations are the most striking feature—hence this stage is sometimes described as " meningeal." This stage gives place to one in which there are manifestations indicative of a selective action on certain parts of the nervous system—particularly, but not exclusively, the anterior horn cells of the spinal cord—with resulting paralysis of a flaccid type.

(*a*) **The Meningeal Phase.**—It is important to emphasise again that this stage may be absent. If it occurs it is *usually* mild, rarely severe and may last from a few hours to a few days. Sometimes the disease " aborts " after *this* stage, although the term *abortive* is now restricted to cases which do not advance beyond the initial stage. The terms, *non-paralytic poliomyelitis* or *meningeal type of poliomyelitis* are used instead. In this stage objective signs first appear in the nervous system.

Pyrexia is usually moderate (101° to 104° F.). The child is mentally bright, flushed and, sometimes, the whole body is pink. Apathy, drowsiness, insomnia and irritability may be present. A coarse intention tremor is sometimes seen. Sensory symptoms are of frequent occurrence at this stage, but disappear later. *Headache* is often severe. *Pain* is common : it may be spontaneous or provoked by movement or pressure on the muscles ; combined with *hyperæsthesia*, which is sometimes present, this results in tenderness on handling the affected parts, and apprehension at the approach of an examiner. These sensory manifestations may be generalised—limbs, back and neck—or localised to a limb, when they may presage a paralysis of that part. The most valuable objective sign is *stiffness of the spine or neck*. Any attempt at flexion provokes resistance. Active movements, which normally involve flexion of the spine, such as sitting

up in bed, are carried out in such a way as to avoid flexing the rigid spine ; the patient supports himself with his hands placed far behind him in the bed (Amoss' sign). The head is retracted, but flexion is not grossly resisted until the movement is communicated to the spine, *i.e.*, until the chin is almost upon the chest. Retention of urine sometimes occurs. The reflexes are not very helpful, except when absence or inequality on the two sides point to a definite organic lesion. The tendon reflexes are often brisk in this stage, but if depressed or absent, usually herald the onset of paralysis. The same uncertainty may exist with the abdominal reflexes, which are, however, usually retained. The plantar reflexes are usually flexor, occasionally extensor, particularly in cases associated with sphincter disturbances.

In this stage abnormalities of the *cerebrospinal fluid* are present, but whilst they are suggestive, they are not pathognomonic. The fluid is clear, colourless or slightly opalescent (ground glass), and is usually under increased pressure. There is a moderate *pleocytosis* of 50 to 100, sometimes more, per centimetre. The cells *at this stage* usually include a percentage of *polymorphonuclears*, which may actually be in the majority. Protein is normal or only slightly increased, and sugar and chlorides are practically normal. As the disease advances into the paralytic stage the number of cells *decreases*, the type rapidly changes to *lymphocytes* or other mononuclears and the *protein* increases in amount. The maximum cell count is usually attained in the first week of the disease and often returns to normal within three weeks of the onset, whereas the increase in protein may persist after this has occurred.

When the early meningeal phase occurs without a subsequent paralytic stage the form of the disease is *non-paralytic* or *meningeal* (*vide* Table XXI).

(*b*) **The Paralytic Phase.**—Although there is diffuse involvement of the central nervous system at the beginning of the nervous phase, there is soon evidence that some parts are being more profoundly affected than others. In the vast majority of cases the selective action is upon the spinal cord, particularly the anterior horns of the lumbar and cervical enlargement. Instead of this spinal form, or in addition to it, parts of the medulla or brain may be picked out. This permits an anatomical classification of the disease according to the site of the chief lesion :—

(i) *Myelitic, or spinal form : poliomyelitis :* inflammation of the grey matter of the spinal cord.

(ii) *Encephalitic forms: polioencephalitis:* inflammation of the grey matter of the encephalon, *i.e.*, that part of the central nervous system within the skull.

Varieties are the *bulbar* form—affecting the medulla—the *cerebral* form, and others such as pontine, cerebellar, mid-brain, etc.

(iii) Combinations of any of the above.

Sometimes the disease is further classified according to some prominent symptom. The ordinary spinal form is non-progressive, but a type occurs in which there is a progressive ascending paralysis of Landry's type.

In the unusual *ataxic* form, in which there is lack of co-ordination, ataxia and nystagmus, the site of the chief lesion is uncertain. It may be in Clark's column, the mid-brain or the cerebellum. A *polyneuritic* form, in which the disease resembles neuritis, is also rare.

Spinal Form.

There is usually a relationship between the onset of paralysis and pyrexia. Ordinarily, paralyses appear whilst the patient is still pyrexial, but shortly after they are established—within three or four days as a rule—the pyrexia subsides. As a corollary to this, it may be said that as long as there is pyrexia there is danger of paralysis appearing, and that when the temperature has subsided this danger is less likely. Nevertheless, paralyses sometimes appear just after the temperature has dropped, and in rare instances may be delayed for some days. As a rule, meningeal or sensory manifestations disappear with the pyrexia, and then the chief—often the only—feature is *paralysis*. It happens occasionally that all the previous manifestations of the disease including pyrexia are so slight or insignificant that the first sign of the disease is the onset of paralysis.

When paralyses appear they do so almost simultaneously (twenty-four to forty-eight hours) so that they are *maximal at the onset.* They remain stationary for a variable time, but, as a rule, after a week or two the less severely affected parts begin to improve.

Since the damage mainly affects anterior horn cells, paralyses are of lower motor type, *i.e.*, flaccid paralyses with loss of tendon jerks. Depending upon the degree of damage there may be simple weakness (paresis) or complete paralysis. The whole of the body may be completely paralysed from the neck downwards, but as a rule the damage is much less

extensive and rarely uniform. The lower limbs are more frequently affected than the upper limbs or the trunk. The damage may affect one limb, usually a lower one (monoplegia), or one lower and one upper limb—on the same or on opposite sides, or both lower limbs (paraplegia), or all four limbs (quadriplegia). When a limb is involved, it is seldom that all the muscles are affected, *i.e.*, the limb is not completely paralysed. It is a common tendency of poliomyelitis to pick out groups of muscles, so that the paralysis is "patchy." In the lower extremity the extensors of the knee (*e.g.*, quadriceps femoris), the dorsiflexors of the ankle (*e.g.*, tibialis anticus) and the peroneal group of muscles are most commonly involved. In the upper limb the deltoid is most frequently affected. In the trunk the weakness or paralysis may involve the abdominal muscles, the muscles of the back, the intercostals, or the diaphragm. When the respiratory muscles are affected difficulty in breathing may become dangerous. Respiratory failure or secondary broncho-pneumonia is, in fact, the commonest cause of death in the spinal type, and if the muscles of respiration are not affected, the prognosis as to life is good. The paralysed muscles are limp and flaccid. Tendon jerks are diminished or absent. If the paralysis persists, wasting sets in and marked atrophy is present within two months.

Progressive Spinal Forms.

Occasionally the paralyses do not appear simultaneously but are progressive. In Landry's type the paralyses *ascend* rapidly. They begin in the legs and, spreading upwards, involve in succession the abdomen, back, upper limbs, neck, bulbar nerves and finally the centres in the medulla, particularly the respiratory centre. Death usually takes place in a few days. In rare instances the paralyses stop part of the way up and recede in the reverse direction, *i.e.*, downwards. A still rarer progressive *descending* form also occurs.

Bulbar Form.

This term is applied to those types in which the chief manifestations are the result of damage to the medulla and neighbouring structures—the pons and mid-brain. Purely bulbar forms are rare. Usually there is evidence of damage elsewhere—either in the spinal cord (bulbo-spinal form) or higher in the nervous system—the cerebrum or cerebellum. In bulbar forms the manifestations are the result of involvement of the nuclei of cranial nerves and of medullary centres. The

commonest nuclei affected are the seventh (facial), usually unilateral and causing facial paralysis; the ninth (glosso-pharyngeal), causing pharyngeal paralysis with difficulty in swallowing, or palatal paralysis with nasal voice and regurgitation of fluids and food through the nose; the sixth (abducens), causing squint and diplopia; the third (oculomotor), causing internal and external ophthalmoplegia, usually partial; and the twelfth (vagus), causing disturbances of respiratory and cardiac action and laryngeal paralysis. Dyspnœa from involvement of the bulbar respiratory centre is more dangerous than that due to spinal damage, and death is the usual outcome.

In the rare *cerebral* form, convulsions, vomiting, spastic paralysis and exaggerated reflexes are the usual symptoms. In the *ataxic* type, loss of co-ordination, ataxia and nystagmus occur.

Relapses and Recrudescences.—Recurrence of symptoms with extension of paralyses occasionally occur one to twelve weeks after the first paralysis, and may result in death; but true second attacks are extremely rare as the immunity conferred by the disease is usually solid.

Differential Diagnosis.

The *initial systemic phase* may be confused with *infections of the upper respiratory tract,* such as coryza, tonsillitis, bronchitis and influenza, and with *gastro-intestinal disorders* such as gastro-enteritis or even acute appendicitis. Diagnostic errors may operate in either direction. During epidemics there is a tendency to suspect poliomyelitis in respiratory or gastro-intestinal disorder. If paralyses do not subsequently appear, the case is called abortive, and this diagnosis cannot be disputed since the manifestations may be identical. Actual confirmation of poliomyelitis is impossible unless the nervous phase develops. On the other hand, cases of poliomyelitis may be diagnosed as respiratory or gastro-intestinal disorders, and it is only when nervous manifestations appear that the true diagnosis becomes apparent. If they do not appear, the case is truly abortive and the fact that the patient has suffered from an infection with the virus of poliomyelitis is never known. These abortive cases, which are not uncommon, are partly responsible for difficulty in tracing the spread of the disease.

If a *meningeal* phase occurs, it has to be differentiated from other inflammatory conditions of the nervous system, *i.e.*, from *meningitis* and *encephalomyelitis*. In *meningitis* muscular

rigidity is generally more marked and persistent, hyperæsthesia is not prominent, and paralyses of the limbs, if they occur at all, are late. In poliomyelitis, meningeal signs are seldom marked and are usually transient; hyperæsthesia is often a prominent symptom and flaccid paralyses of the limbs are common and early. In *epidemic encephalitis* the emphasis is upon the mental symptoms, especially the presence of insomnia and lethargy; focal lesions are disseminated; pupillary and ocular signs are common; paralyses of the limbs unusual; but abnormal movements are frequent. Epidemic encephalitis is more likely to be confused with the bulbar and cerebral types of poliomyelitis, but even in these, pupillary and ocular anomalies are not so frequent, and abnormal movements and Parkinsonism practically unknown.

From examination of the cerebrospinal fluid purulent meningitis can be easily excluded, but differentiation of other conditions is much more difficult. Poliomyelitis, encephalitis lethargica, post-infectious encephalomyelitis and tuberculous meningitis all produce fluids which resemble one another fairly closely (see Table XVIII). Distinctly low chloride content is strongly suggestive of *tuberculous meningitis*, and the detection of tubercle bacilli, although positive evidence, is not always possible. In tuberculous meningitis the onset is usually insidious in a child who has been previously unwell; the disease evolves slowly; flaccid paralyses of the limbs are uncommon; and ocular palsies frequent. In *post-infectious encephalomyelitides* diagnosis largely depends upon knowledge of a recent or existing infectious disease and here again flaccid paralyses are uncommon. It will be seen that the existence of paralysis is a valuable differentiating sign, and when the diagnosis cannot be made with certainty in the meningitic phase of poliomyelitis, the development of flaccid paralyses in the course of a day or two usually clinches the diagnosis.

Tenderness of the limbs, which is not uncommon in the meningeal phase of poliomyelitis, may result in confusion with *rheumatic fever* and with *infections of bones, joints and muscles.* In these there are no abnormal signs in the central nervous system, the cerebrospinal fluid is normal, and there are no true paralyses. Rheumatic fever runs a more protracted course and the pains and pyrexia respond to salicylates. *Torticollis* produces stiffness of the neck, but the condition is local and usually unilateral.

Once the typical *paralyses* appear there is seldom difficulty in diagnosis; but sometimes other conditions accompanied by paralyses or pseudo-paralyses are mistaken for poliomyelitis.

Reluctance to use the limbs in *rickets, scurvy* and the *acute epiphysitis* of congenital syphilis may suggest paralysis and an erroneous diagnosis of poliomyelitis be made. In rickets the sweating of the head at night, beading of the ribs, frontal bossing and craniotabes, curvature of bones, Harrison's sulcus and X-ray appearances are diagnostic points of value. In scurvy there is often swelling of the limbs, *e.g.*, at lower end of femur, and tenderness is extreme, so that the infant screams when touched or moved. Swollen and bleeding gums are sometimes found in those with teeth, and the X-ray appearances of the bones are frequently diagnostic. Syphilitic epiphysitis occurs early in life (in the first few weeks), other signs of congenital syphilis may be present, the Wassermann reaction is often positive and X-ray changes are diagnostic.

Prognosis, Cause of Death and Case Fatality Rate.

If the diagnosis is made in the preparalytic stage it is of considerable value to be able to foretell the course of the disease. This cannot be done with any accuracy, but the cell count in the cerebrospinal fluid may be of some help. High counts are usually but not invariably associated with more severe attacks than low counts. Prognosis is intimately bound up with paralysis. Death does not occur unless paralyses appear, and if they do there are two matters of concern: (i) prognosis as to life; (ii) prognosis as to recovery of paralysed muscles.

Prognosis as to Life.—The outlook is always best for those aged from one to ten years, although the case fatality rate varies in different epidemics. The frequency of abortive cases during epidemics and the diagnostic difficulties they present have been mentioned. If rates are based only upon cases with involvement of the nervous system, the figures vary between 5 and 25 per cent. in different epidemics. Prognosis also depends upon the main site of the disease: bulbar types are much more fatal than spinal and the progressive form is almost invariably fatal.

The usual causes of death are :—

(i) *Respiratory Failure.*—In the spinal form this is due to paralysis of the intercostals and diaphragm from involvement of the dorsal and cervical cord, and in the bulbar form to failure of the medullary centres. Respiratory paralysis of spinal origin is much more amenable to treatment in the Drinker respirator than that of bulbar origin. Death usually occurs

in three to six days from the onset of the paralysis, but in severe bulbar forms it may take place within forty-eight hours.

(ii) *Broncho-pneumonia* is secondary to paresis of the respiratory muscles or is the result of aspiration in bulbar cases with pharyngeal paralysis. Death usually occurs later—in from ten to fourteen days. The toxæmia of the disease itself is not sufficient to cause death.

Prognosis as to Recovery in Paralysed Muscles.—Muscles which show only paresis usually recover. As long as there is any power left, the chances of recovery are good. Of those which are completely paralysed, some will recover entirely, some be left weak and some remain permanently paralysed. It is a rule that the extent of involvement of the nervous system is much greater than the clinical features suggest, and the extent of the initial paralyses is much greater than the residual muscular damage—which, indeed, may not result at all. When recovery sets in, it is fairly rapid at first and gradually slows down. It is therefore possible to obtain a rough conception of the amount of permanent damage quite early. Recovery may begin as early as a week after the onset, and in about ten to twenty-one days the reactions of degeneration appear in the more seriously affected muscles. Return of power is variable in degree and rate ; improvement may occur as long as two years after the onset, so that ultimate damage cannot be estimated with certainty till then.

Electrical Reactions.—The normal muscle exhibits certain contractions when its motor point (*i.e.*, the point at which the nerve enters) or the nerve itself is stimulated by electric currents. The types of current used are *faradic*, an interrupted current which produces a rapid succession of stimuli of very brief duration, and *galvanic*, which is a continuous current. The faradic current causes a tetanic contraction ; the galvanic current produces a quick twitch on starting (*i.e.*, on closing the circuit) and on stopping (*i.e.*, on breaking the circuit), but not when the current is running constantly. This twitch occurs whether the anode or the kathode is used for testing, but the response varies. Normally the kathodal closing contraction is greater than the anodal closing contraction (K.C.C. $>$ A.C.C.).

If there is a *lower motor neurone* lesion, as in poliomyelitis, the muscle wastes and the responses to the current may alter. These changes are described as *reactions of degeneration* (R.D.). They may be *partial*, indicating that some of the fibres of the muscle remain unaffected, or *complete*, indicating that they are all involved. In the mildest cases the reaction of the *muscle* to faradism is weak or absent

but the reaction to galvanism although persisting is sluggish. Such muscles usually recover. In more severe cases the *nerve also* fails to respond to faradism, and such cases often recover also. When the reaction to degeneration is complete there is, in addition to inactivity to faradism, a failure to respond to galvanism, either in the nerve or in the nerve and muscle. Furthermore, there may be polar changes, the anodal closing contraction being greater than the kathodal closing contraction (A.C.C. > K.C.C.). The prospect of recovery in such cases is very poor. Thus failure to respond to galvanism is of much more serious import than failure to respond to faradism. Some muscles show no reactions of degeneration and in them recovery is almost certain.

Chronaxie.—Another method employed for testing reactions of degeneration is by chronaxie. A current of a particular strength (which is calculated separately for each muscle) is passed through the muscle or nerve and the minimum *time* for which it must flow before it produces a contraction is the *chronaxie* of that muscle. Degeneration of the nerve results in a considerable increase in this time. The method is more precise than the one described above, and signs of degeneration and regeneration can be detected earlier than by the usual method.

Sequelæ.—Poliomyelitis is a crippling disease and three types of permanent damage commonly result :—

1. *Muscular.*—Permanent paralysis or paresis result in a wasted flail limb with poor muscular power.
2. *Trophic.*—The permanently damaged limb fails to grow at the same rate as the healthy fellow ; the circulation is poor and chilblains may occur.
3. *Deformities.* — Weakness, contractions in unopposed healthy muscles, and failure of the limb to grow cause deformities.

Treatment.

1. GENERAL MEASURES.—In all probability poliomyelitis is infectious only in the first few days of the illness, but in the absence of definite knowledge it is wise to isolate the patient for four weeks. The usual measures for the care of a patient suffering from an infectious disease are necessary (see Chapter X, p. 79). *General rest* for four to six weeks is essential. All pain and tenderness should have been absent for at least a fortnight. The *special rest* for the paralysed muscles may, however, keep the patient in bed much longer (see (3) and (4) below). Symptomatic treatment usually consists in the relief of pain and the inducement to sleep. A sagging mattress causes stretching of the spinal roots and may be avoided by the use of fracture boards inserted under the mattress. Because of the prolonged immobilisation, care of the skin is particularly important. Analgesics such as aspirin and codeine, and

hypnotics such as chloral and luminal, may be given. An ice-bag often provides relief from headache and pain in the neck.

2. SPECIFIC MEASURES.—Convalescent serum is now generally regarded as useless in therapy, but is still given by some in the preparalytic stage in doses of 50 c.c. intravenously. Drugs such as urotropine, which reach the cerebrospinal fluid, are also considered valueless. Drainage of the subarachnoid space has been used as a therapeutic measure, but its chief value is for the relief of meningeal symptoms and the collection of cerebrospinal fluid for diagnosis.

3. TREATMENT OF THE PARALYSED MUSCLES IN THE ACUTE STAGE.

(*a*) *Immobilisation in Proper Position.*—Rest, avoidance of stretching and prevention of deformities—three important principles—are secured by *immobilising* the paralysed part in a position of *relaxation* by means of light retentive apparatus such as sandbags, splints, pads and slings. Frames, *e.g.*, Jones' hip frame, are sometimes used. Plaster of paris is generally considered unsuitable in this stage. If a paralysed muscle is allowed to remain stretched, its functional recovery is unlikely because it may fail to regain the normal postural tone necessary for co-ordinated voluntary movement. Deformities result from the effect of gravity and the unopposed action and subsequent contraction of unaffected muscles. The positions which must be maintained in paralysed parts are those described below, although variations may be necessary depending upon the muscles affected: *hip*, extended and slightly abducted; *knee*, extended; *foot*, dorsiflexed to right angle and neutral; *shoulder*, abducted to a right angle and externally rotated; *elbow*, flexed to a right angle if the biceps is weak and extended if the triceps is weak; *forearm*, midway between pronation and supination; *wrist*, dorsiflexed; *fingers*, extended. In the *trunk* scoliosis is prevented by sandbags. Splinting is irksome and unnecessary immobilisation may be harmful, so that modification in the direction of less splinting should be introduced as soon as it is safe to do so.

(*b*) *Maintenance of Circulation* by local heat is sometimes employed. It may be provided by wool wrapped around the limb, by radiant heat baths, or by diathermy.

4. TREATMENT DURING THE STAGE OF MUSCLE RECOVERY.—The duration of the period of recovery is very variable, but as it may last for two years, treatment should be continued for the whole of this time. As soon as the acute stage is over—when muscle tenderness has gone—an estimate of the damage should be made, the muscle graded and a record kept. Regular re-examination and recordings on a "muscle chart" permit an accurate estimate of progress to be made.

Treatment aims at increasing power in all muscles showing any residual functional capacity. The *maintenance of circulation* by radiant heat and massage, *re-education* of the muscles by carefully graded exercises in water and in air, are the most important measures. The stage at which they should begin is still subject to controversy. The orthodox practice is to be cautious, on the ground that too early activity is harmful. The value of hydrotherapy lies in the buoyancy of the water, which diminishes the effects of gravity and permits the patient to carry out movements not possible in the air; the warmth of the water is also beneficial to muscular contraction. It is of the greatest importance to *avoid fatigue*, both local and general, during muscle training. During this stage the patient should be allowed up, provided weak muscles can be protected from undue strain by suitable apparatus.

In contrast to orthodox practice, Kenny avoids the generally accepted methods of immobilisation by splinting, whilst accepting the importance of proper position. She emphasises the importance of a bright mental outlook, maintenance of the circulation, hydrotherapy, muscle-re-education introduced *as early as possible*, even before the cessation of pain, and maintenance of "impulse." Hydrotherapy is carried out in individual slipper baths or in special arm baths; a warm bath is used with a hot and cold douche as a method of stimulation; the limbs are exercised in the bath. Re-education consists essentially of passive movements, the child being invited to assist, if possible, by voluntary contraction of the appropriate muscle. Maintenance of "impulse" implies the mental effort to carry out a movement, even when the muscles are so paralysed that no contraction can be perceived.

5. TREATMENT OF PERMANENT DISABILITY.—The student is referred to textbooks of orthopædics for the various operative and non-operative measures for the relief of permanent disability.

6. TREATMENT OF RESPIRATORY FAILURE.—For respiratory failure *continuous artificial respiration* must be maintained until the muscles recover. If they do not, but the patient survives,

he is condemned to a mechanical respirator for the rest of his life. When paralysis is due to involvement of the medullary centres, prognosis as to life is much graver, as other vital centres are commonly involved; but if the patient survives, complete recovery is the rule. In spinal forms, lower centres are affected; prognosis as to life is better, but permanent residual paralysis may occur.

Mechanical Respirators are employed for prolonged artificial respiration. These have been used for respiratory failure in poliomyelitis, diphtheria, asphyxia neonatorum, alcoholic coma and drug poisoning. Mitman and Begg (1934) have also used them for pulmonary collapses and to re-expand a lung after operation for empyema.

Three types are used :—

1. APPARATUS PRODUCING NEGATIVE EXTERNAL PRESSURE, *e.g.*, Drinker, Both, Burstall, cuirass. The principle involved is to apply a negative pressure to the thorax rhythmically, sixteen to twenty times a minute, so that the thorax expands and air enters the lungs through the nose and mouth—thus inducing *inspiration*. The elastic recoil of the chest in the intervals results in expiration. In the Burstall and cuirass types the thorax only is enclosed in an airtight light metal jacket in which the pressure is reduced by 16 to 18 cm. of water at regular intervals by means of an electrically driven suction bellows. In Drinker and Both (box) types the whole body below the neck is enclosed in an airtight chamber attached to a similar bellows.
2. APPARATUS PRODUCING POSITIVE EXTERNAL PRESSURE, *e.g.*, Paul-Bragg pulsator. The thorax is enclosed in a rubber bag into which air is forced rhythmically by a bellows. The pressure on the thorax induces *expiration* and the elastic recoil of the chest allows inspiration to occur.
3. APPARATUS PRODUCING POSITIVE INTERNAL PRESSURE, *e.g.*, M'Kesson resuscitator. A mask applied over the mouth and nose permits oxygen and CO_2 to be forced into the respiratory tract. This apparatus is commonly employed as a temporary measure, *e.g.*, when the patient is removed from a box respirator for necessary nursing or medical attention.

In poliomyelitis the patient must be put into the respirator as soon as respiratory paralysis is suspected, otherwise

broncho-pneumonia may develop. Treatment must be continuous for days or weeks. If pharyngeal paralysis is also present the foot of the respirator should be tilted up, so that drainage of mucus through the nose can occur. Mucus may also be removed by digital swabbing or by the use of an electrically operated aspirator. The respirator should be adjusted to give a rate of artificial respiration of sixteen to twenty per minute. In patients who respond satisfactorily the respiratory rate adjusts itself to that of the machine, dyspnœa and cyanosis disappear and restlessness subsides.

Prophylaxis.—The presence of immune bodies in the sera of convalescents can be determined by tests on monkeys—the serum being used to neutralise the virus before inoculation. Convalescent serum (10 c.c.), adult immune serum (20 c.c.) and whole blood (50 c.c.) are used for passive immunisation. Active immunisation has been tried but is not to be recommended.

SUMMARY OF CHAPTER XXV

Forms.

(i) Myelitic (spinal).
(ii) Encephalitic (polioencephalitis) : (*a*) bulbar, (*b*) cerebral, (*c*) ataxic.
(iii) Ascending.

Phases.

(i) Initial (pre-CNS invasion). Respiratory and gastro-intestinal symptoms.
(ii) Latent period.
(iii) Nervous.
- (*a*) Meningeal symptoms : preparalytic stage, changes in C.S.F.
- (*b*) Paralytic stage : flaccid paralyses with loss of jerks.

(iv) Sequelæ : Thin, wasted, weak or paralysed short limb with poor circulation.

Types.—Abortive, non-paralytic, paralytic, with or without permanent damage.

Treatment.

Acute Stage : Immobilisation in a position of relaxation.
Recovery Stage : Re-education and maintenance of circulation.

CHAPTER XXVI

EPIDEMIC ENCEPHALITIS

ENCEPHALITIS LETHARGICA

DEFINITION.—An acute or subacute virus infection of the nervous system, characterised clinically by febrile catarrh and disseminated lesions in the nervous system. The nervous manifestations are very variable and several types of the disease probably exist, of which two are fairly clearly defined but cannot be sharply differentiated. Type A, the "original" *encephalitis lethargica*, is more chronic and more variable in its course and more likely to exhibit sequelæ; its chief nervous symptoms are lethargy, ocular palsies and a liability to subsequent Parkinsonism. Type B is more acute and complete recovery is more frequent.

Epidemiology.—Although there is historical evidence that the disease is not new, modern knowledge dates from the extensive epidemic which occurred during the Great War. Cases first appeared in Rumania (1915) and France (1915-16), but it was not until von Economo's account of an outbreak of lethargic encephalitis in Vienna in the winter of 1916-17 that it was recognised as a clinical entity. From Central Europe the disease spread to Australia, Great Britain and the United States in 1917-18. Since then epidemics have occurred in many parts of the world. The biggest epidemic in England occurred in 1924. In recent years the disease has largely died out, but sporadic cases still occur.

The original *encephalitis lethargica* was Type A. When it became evident that lethargy was not a constant symptom, the term *epidemic encephalitis* was introduced. Later, Type B was recognised in Japan (1924, 1929, 1935) and St Louis (1933), although there were differences in the diseases in these two places.

Type A, although occurring throughout the year, is more prevalent in winter and spring, whereas Type B occurs notably in the late summer and autumn.

Like cerebrospinal fever and poliomyelitis, direct spread from case to case (*e.g.*, in the same household) is rarely seen.

It is therefore probable that abortive cases and carriers exist and that transmission occurs through droplets. Persons of all ages are affected by both types, but Type A is more frequent in adults and Type B in children and adolescents. Fatality increases with age. The rate varies from 7 to 40 per cent. in different outbreaks.

Pathology.—The clinical picture, the pathological changes in the brain, the experimental work on animals and the epidemiological features suggest that the disease is a virus infection of the nervous system. Because the virus of herpes febrilitis can produce a specific herpetic meningo-encephalitis in rabbits resembling encephalitis lethargica in man, it was believed that an ætiological relationship existed between the two diseases. The viruses are probably not identical (Stern, 1928, 1930). There is evidence that the viruses of the different types (Type A, St Louis, and Japanese) are also slightly different. The virus of the Japanese type has now been grown on the chorio-allantoic membrane of a developing chick (Kawakita, 1939).

The condition is a diffuse inflammation of the brain, most marked in the basal ganglia, mid-brain and pons. The naked eye changes are slight ; congestion, sometimes small hæmorrhages or even extravasations, and a pinkish colour to the grey matter. Microscopically the grey matter is chiefly affected in an inflammatory reaction with neuronal degeneration and subsequent gliosis, but the distribution is patchy.

(i) *Vessels.*—At first there is merely congestion with occasional hæmorrhages. After ten days, infiltration of the walls and perivascular spaces with cells, chiefly mononuclears, results in the characteristic *perivascular cuffing*. The more chronic the case the more marked are these changes.

(ii) *Nerve Cells.*—The degeneration particularly affects the cells, especially those containing melanin, in the sites mentioned above.. In the progressive type with Parkinsonism, the *substantia nigra* of the mid-brain is most damaged and there is evidence that the process is still active, though chronic.

(iii) *Glial nodes* may be found later replacing destroyed nerve cells.

Incubation period : from **four** to **twenty-one** days.

Clinical Features.—The onset may be gradual or sudden ; usually it is insidious with prodromal symptoms that are not characteristic. Rarely it starts with an abrupt neurological

manifestation such as a fit (apoplectic or epileptic), vertigo, headache or severe pain.

Constitutional symptoms vary from mild indisposition, sometimes so trivial as to be overlooked, to a profound toxic state. The commonest prodromata are febrile catarrh, malaise, anorexia, headache, generalised pains and slight gastro-intestinal disturbance (vomiting and constipation—occasionally diarrhœa). Rarely an erythema of the skin appears. Within a day or two *ocular palsies* and *lethargy* may occur, and these, with the *pyrexia*, constitute a common triad of signs. *Pyrexia* is usually irregular, moderate in degree and of short duration ; it may be trivial or absent ; sometimes it persists for weeks ; occasionally it appears late. Hyperpyrexia sometimes occurs. In severe lethargic cases the temperature usually rises before death.

Manifestations referable to the *nervous system* are, however, numerous and are conveniently classified after Walshe (according to Hughling Jackson's terminology) into *positive*, denoting an exaltation of function from irritation or removal of higher control, and *negative*, denoting depression of function. In the earlier outbreaks (Type A) negative signs predominated ; but all combinations of positive and negative may occur, and the chief groups are as follows :—

	POSITIVE.	NEGATIVE.
Sensory	Headache. Muscular pains. Neuralgic pains.	... ...
Mental	Restlessness ; delirium. Insomnia.	Lethargy.
Muscular	Rigidity (including Parkinsonism). Involuntary muscular movements.	... ... Paralysis (particularly ocular).

Headache, frequently occipital, is a common early symptom and may become persistent and troublesome.

Lethargy is one of the *disorders of sleep* which occur in this disease. Although absent in certain types, *e.g.*, where positive symptoms predominate, it is a common manifestation and characteristically occurs in association with paralysis. It varies from slight drowsiness to coma. The patient can often be roused to answer simple questions and take food, but quickly relapses into his sleepy state. Lethargy may be transient, or last for days, weeks or even months. Sometimes

it is slowly progressive ; at others it is intermittent ; rarely it first appears during a recrudescence.

A common association, particularly in children, is somnolence by day and wakefulness, even delirium, at night. This *reversal of the sleep rhythm* is almost pathognomonic and may persist as a sequel. In some outbreaks *insomnia*, not lethargy, is the prominent feature, and is associated not only with wakefulness but with nocturnal exacerbation of other manifestations, such as pain, choreic movements, respiratory disorders and mental symptoms.

Ocular Palsies.—Of cranial nerve palsies the most constant and characteristic are ocular. They appear early in the disease and are valuable diagnostic signs, and occasionally may be the sole symptom. Weakness of ocular movements results in *diplopia* and *squint*. *Ptosis* and *nystagmus* are common. All forms of external and internal ophthalmoplegia have been recorded, but the third nerve is more commonly affected than the fourth or sixth. Ocular palsies often vary from day to day and may be transient. Permanent paralysis is rare. Other cranial nerves are occasionally affected. The facial muscles may lose tone and the normal folds and wrinkles become smoothed out. When associated with ptosis and lethargy a dull, expressionless appearance is produced which may be in marked contrast to the mental lucidity.

Positive Excitomotor Phenomena.—These irritative manifestations may assume various forms and are a prominent feature of *myoclonic types*. They may be early or late. *Muscular contractions*, sometimes rhythmic, may involve a few fibres only and be so slight as to pass unnoticed by the patient ; or whole muscles may be involved and painful cramps or movements of the limb result. Contractions may occur in any part of the body, or be restricted to particular areas. The neck, thorax and abdominal muscles are commonly involved. *Choreiform* movements (usually associated with delirium), *athetoid* movements and *Jacksonian fits* sometimes occur. *Hypertonus* (rigidity) is a feature of *Parkinsonism* (*vide infra*). *Catatonia* (limbs remain indefinitely in the attitude in which they are placed) is not uncommon in the acute stage.

Sensory Manifestations.—Although signs of meningeal irritation (headache and stiffness of the neck) and severe muscular and neuralgic pains are not uncommon positive symptoms, sensory loss is rare.

Reflexes.—The changes in the reflexes are not constant. Often the tendon reflexes are diminished or absent, but may be normal or exaggerated. The plantar reflexes are usually

flexor and the abdominal reflexes present. The pupils may be normal in size, contracted, dilated, equal or unequal. The reactions to light, accommodation and convergence may be normal, impaired or absent, and may differ on the two sides.

Mental disturbances, common in the early stages, such as insomnia, delirium and lethargy, are mentioned above. Rarer ones, and late mental manifestations, are considered below.

Cerebrospinal Fluid.—From Table XVIII (p. 283) it will be seen that there are no characteristic changes in the cerebrospinal fluid, which is normal or nearly so. Any marked departure is to be taken as evidence against a diagnosis of epidemic encephalitis.

Blood Picture.—A moderate leucocytosis is common, but is not invariable.

Late Manifestations (*the Chronic Stage, Post-Encephalitic Syndromes, Sequalæ*).—The conditions enumerated below may be early, *e.g.*, within a few days of onset, but are usually late phenomena and may be delayed for months. Not infrequently a quiescent interval occurs between the early manifestations of the acute stage and the late manifestations of the chronic stage. Sometimes late phenomena appear in patients in whom the initial pyrexia and nervous signs were so slight as to be neglected ; occasionally no suggestion of such an illness can be elicited. In some types of the disease (*e.g.*, Type B) and in certain outbreaks sequelæ are rare. Von Economo (1931) distinguishes between protracted states of convalescence, residual states which remain after the acute phase has passed, and chronic post-encephalitic diseases.

(i) **Parkinsonism** is the most frequent of the chronic syndromes. Although resembling senile paralysis agitans (Parkinson's disease) differences exist between the two. Muscular rigidity, loss of associated and automatic movements and tremor are the cardinal signs. The whole body may be affected, but the face is involved early (Parkinsonian mask). The facial muscles are rigid, the mouth half-open, the swallowing reflex inhibited causing dribbling of saliva, and the blinking reflex diminished ; the result is a staring, expressionless, stupid face. Speech is slow and the voice monotonous. Rigidity of the trunk and limbs produces a characteristic posture and gait. The head is bowed, the back bent, the elbows slightly abducted and the fingers slightly flexed. The walk is slow and shuffling, and the balance of the patient is easily upset. Tremor is not dominant as in paralysis agitans ; when present, motor efforts sometimes cause a "turmoil of tremor" which is in marked contrast to the quiescent rigidity. *Catatonia* is

common, *e.g.*, a patient lifts a cup halfway to his lips and retains this position for a long period ; or stops in the middle of eating and permits food to remain in the mouth for minutes or hours.

Oculo-gyric Crises, paroxysmal movements of the eyeballs upwards, of sudden onset and lasting for minutes or hours, occasionally occur. Parkinsonism may advance slowly or rapidly or remain stationary.

(ii) **Mental changes** are most frequent in childhood. Disturbances of *sleep rhythm* and *nocturnal excitement*, described in the acute stage, are common residua. Other changes, which may vary from slight to extreme, are mainly in *character* and *disposition*. A quiet, well-behaved and affectionate child may change to an aggressive, quarrelsome and spiteful one ; in extreme cases viciousness and homicidal tendencies may appear. Morbid sexual behaviours and other moral delinquencies, such as stealing, may develop. The various forms of insanity, including inclination to suicide, are, however, rarely of such a nature as to justify certification. Minor changes in temperament, such as apathy, emotionalism, inability to concentrate or work, and loss of memory, are common.

(iii) **Excitor motor sequelæ** are of many forms indicating the diffuseness of the lesions : bradykinesia, choreiform and myoclonic movements, tremors, disturbances in the rate and rhythm of respiration, disorders of the ocular movements, tics and other automatic actions occur.

FORMS OF THE DISEASES.—The manifestations of the diseases are protean. Von Economo (1931) distinguishes the following syndromes or forms in the order of their frequency, but stresses that they may be united in the most varied combinations :—

1. **Acute Forms.**—

A. *Somnolent Ophthalmoplegic* : Onset abrupt, temperature moderate, influenza-like prodromal stage with slight meningeal signs, developing prominent negative signs such as somnolence and ocular palsies.

B. *Hyperkenitic* : Toxic symptoms, motor unrest and positive signs the dominant features ; initial symptoms more severe than in A.

C. *Amyostatic* (*-akinetic*) : Early Parkinsonism and disturbances of sleep function the chief features ; initial symptoms less pronounced than in A or B.

D. *Other forms, e.g.*, monosymptomatic, pseudo-tabetic pseudo-paretic, psychotic, and many *formes frustes* and abortive forms.

2. **Chronic Forms.**—From the many late syndromes two receive special mention :

A. *Parkinsonism.*
B. *Mental states.*

Differential Diagnosis.—1. INFLUENZA.—The epidemic association of the two diseases has been partly responsible for the confusion. In influenza general symptoms, *e.g.*, pains in limbs, pyrexia and rigors, are marked, respiratory manifestations dominant, and neurological signs uncommon ; in epidemic encephalitis general signs are not so marked, neurological manifestations appear and respiratory complications are rare.

2. POLIOMYELITIS AND POLIOENCEPHALITIS.—Confusion is most likely with the cerebral and bulbar forms. The emphasis in poliomyelitis is upon the flaccid paralyses with subsequent atrophy ; the onset is rarely insidious. In encephalitis, although pupillary and ocular signs are common, palsies are transitory, rarely extensive and atrophy is uncommon. Involuntary muscular movements and Parkinsonism, common in encephalitis, do not occur in poliomyelitis. The differences in the cerebrospinal fluid are given in Table XVIII (p. 283).

3. POST-INFECTIOUS ENCEPHALITIDES.—There is an evidence of an existing or recent infectious disease or vaccination, and the onset is commonly very acute with convulsions and loss of consciousness.

4. MENINGITIDES.—Meningeal symptoms progress and become dominant, whereas in encephalitis they become progressively less important. Diagnosis may be difficult and repeated lumbar puncture necessary. A marked pleocytosis of any sort and a low sugar content is against a diagnosis of encephalitis.

5. DISSEMINATED SCLEROSIS in the uncommon acute form may require to be differentiated. The common signs are intention tremor, nystagmus and scanning speech, with definite changes in the reflexes, *e.g.*, Babinski's sign with increased deep reflexes.

6. BOTULISM.—The earliest cases of epidemic encephalitis in England were mistaken for botulism because, in the latter, early bulbar signs are common. The condition is apyrexial with gastro-intestinal symptoms and paralyses.

7. DRUG POISONING.—The difficulty of rousing the patient in the early stages of the illness is uncommon in encephalitis. Chemical examination may be helpful.

8. TYPHUS FEVER.—The exanthem, the Weil-Felix reaction and the cerebrospinal fluid exclude this disease.

9. ENTERIC FEVERS.—The typhoid state is differentiated by the abdominal symptoms, enlargement of the spleen, recovery of the organism from the blood or fæces, and the Widal reaction or its modifications. Difficulty may arise in a patient inoculated against enteric fever who develops epidemic encephalitis (*vide* Chapter XXX, p. 378).

10. OTHER CONDITIONS.—In view of the disseminated lesions and protean manifestations of encephalitis many nervous diseases require to be differentiated. Myoclonic types may simulate *chorea*, and *Sydenham's chorea* is so similar as to be regarded by some as the same disease. Cerebral syphilis, cerebral hæmorrhage, tumours and abscesses of the brain, delirium tremens, hysteria and other functional disorders may be confused. Myoclonic types with abdominal cramps may simulate appendicitis and other abdominal conditions, renal colic, pleurisy and pneumonia.

11. PARALYSIS AGITANS (Parkinson's disease).—Difficulty arises chiefly when there is no history of an acute phase or when the early stage was diagnosed as influenza. Youth, rapid development of rigidity, particularly of the face and neck and a greasy face are in favour of the diagnosis of Parkinsonism. Tremor is more common in paralysis agitans.

Course and Case-fatality Rate.—Recovery may be (i) complete, (ii) complete except for some lasting defect, (iii) incomplete, the condition becoming chronic and progressing either slowly or rapidly ; ultimately it may become stationary or even clear up.

Complete recovery, which is more likely in certain forms of the disease, *e.g.*, Type B, may occur in two or three weeks or be delayed for months. Late manifestations, common in certain forms of the disease, *e.g.*, Type A, tend to become chronic. The patient may be left with defects which do not seriously incapacitate him or pass into a pitiful state of chronic invalidity.

Bad prognostic signs are toxic manifestations such as occur in hyperkinetic forms, and evidence of spread to the medulla (respiratory, cardiac and nutritional manifestations). Death usually takes place in one to three weeks, and is commonly preceded by rising temperature, coma and incontinence. The case fatality rate varies in different epidemics. Including abortive cases and *formes frustes*, Von Economo calculates the rate at 15 per cent. If these cases (not ill enough to go to bed) are excluded the figures become :—

ACUTE STAGE.		SUBSEQUENTLY.	
Death			40 per cent.
Recovery from the acute stage	30 per cent.	Complete recovery	14 ,,
		Recovery with defects but capable of work	26 ,,
Incomplete recovery from acute stage	30 ,,	Chronic invalidity with inability to work	20 ,,

The seriousness of the disease is manifest, but the figures given refer to Type A.

Treatment.—Although case to case spread is extremely rare, the patient should be isolated for a week in the early stages and should remain in bed for two or three weeks after symptoms subside. A water bed should be provided if the illness is protracted. It may be necessary to rouse the patient to feed him; or, in more severe cases, to institute nasal feeding. There is no specific treatment. Von Economo strongly advocates intravenous iodine in large doses, *e.g.*, Pregl's iodine solution: first trial dose, 20 c.c., followed by 50 to 100 c.c. three times a week. Urotropine in fairly large doses is also given. Treatment is, however, mainly symptomatic, hypnotics being most commonly required.

For chronic cases, stramonium or belladonna, pushed to the limit of tolerance, *e.g.*, up to 30 minims of the tincture three times a day, is most favoured. To increase tolerance, pilocarpine nitrate ($\frac{1}{10}$ to $\frac{1}{15}$ gr.) may be added to each dose. Injections of hyoscine hydrobromide ($\frac{1}{150}$ to $\frac{1}{100}$ gr. t.i.d.) are also used.

SUMMARY OF CHAPTER XXVI

Cause: Virus, causing febrile catarrh and disseminated lesions of the nervous system.

Types:

A. Less acute; more liable to sequelæ.
B. More acute; complete recovery more likely.

Chief Forms:

1. Negative signs dominant: lethargy, ocular palsies, liability to subsequent Parkinsonism.
2. Positive signs dominant.

Sequelæ: Parkinsonism and mental states.
Treatment: Symptomatic.

CHAPTER XXVII

INGESTION DISEASES

THE ingestion diseases here described are all acute alimentary infections and may be classified as follows :—

1. Those due to known specific organisms, *e.g.*, the enteric fevers, the dysenteries, cholera, certain types of food infection and poisoning, some cases of infectious enteritis in children.
2. Those due to unknown organisms, *e.g.*, *most* cases of infectious enteritis in children.
3. Those in which organisms are found, but whose significance is uncertain, as in certain types of infectious enteritis.

Occasionally diseases which are usually due to *inhalation* may result from *ingestion*, *e.g.*, outbreaks of scarlet fever are sometimes due to the ingestion of infected milk (*vide* Chapter XII).

The organisms responsible for the ingestion diseases belong to various genuses, *e.g.*, vibriones are responsible for cholera, staphylococci occasionally produce food infection, but the vast majority of them belong to the genus *Bacterium*.

The members of the genus *Bacterium* are typically intestinal parasites. They are gram negative, non-sporing rods, often motile, readily cultivated on artificial media. They are difficult to distinguish from one another morphologically, but they produce fermentation reactions which are of considerable value in differentiation. A fundamental division of the groups is possible because of their behaviour to *lactose*. Generally the lactose-fermenting organisms are *non-pathogenic* and include such normal inhabitants of the bowel as *B. coli*. *The non-lactose fermenting organisms include almost all the pathogens*, and, following Topley and Wilson (1936), are grouped as follows :—

1. The **Salmonella** sub-group, which includes :

   (*a*) *Bact. typhi*—responsible for typhoid fever.
   (*b*) *Bact. paratyphi A, B and C* (*Hirschfeld*)—responsible for paratyphoid fevers.

(c) *Bact. typhi-murium* (*Bact. aertrycke*)—responsible for certain types of food infection in man, although it typically produces an enteral infection in mice.

2. The **Dysentery** sub-group which includes *Bact. shigæ* and *Bact. flexneri*, responsible for dysentery. An important exception in this group is *Bact. sonnei*, responsible for a type of dysentery, which is a late lactose fermenter, *i.e.*, it ferments lactose, but slowly.

Motility of the organism is another valuable differentiating property, *e.g.*, the typhoid bacillus is always *motile*, whereas the dysentery bacillus is *non-motile*. In the final differentiation of members of the genus, *agglutination tests* are employed. Certain species, *e.g.*, some *paracolon bacilli* which also belong to the genus *Bacterium*, and which are usually lactose fermenters, are considered pathogenic because they have been recovered from cases of acute enteritis.

One member of the *genus proteus* (which belongs to the same tribe as bacterium), the *Proteus morgani*, is sometimes found in large numbers in infants suffering from acute enteritis, but its significance is uncertain. Many observers believe it the causal organism.

The diseases considered here have certain features in common. The *mode of infection* is the same in all of them. The causal organism gains entry to the alimentary canal as the result of the ingestion of infected food or drink (particularly water and milk) which has been contaminated, directly or indirectly with infected excreta, *i.e.*, they are bowel to mouth infections. In all of them *diarrhœa* is the most constant clinical manifestation, although it does not invariably occur. Aids to diagnosis usually consist in examining the stools for the causal organism and the blood for the presence of antibodies.

Intestinal *carriers* occur and, given suitable opportunities, are liable to initiate outbreaks of the disease. When such occur, whether in the form of a widespread epidemic or restricted to a locality or an institution, they may assume one of two forms :—

(i) *Explosive* outbreaks, in which a number of people are affected more or less simultaneously, so that no direct connection can be traced between cases, but all are due to a common source, such as the ingestion of the same infected article of diet.

(ii) Outbreaks in which the disease *spreads from case to case,* and in which the connection can often, but not always, be traced.

Sometimes epidemics exhibit both features. Generally, however, these diseases occur sporadically to-day. The decline in epidemics can be attributed largely to modern methods of sanitation and hygiene, so that infected excreta are properly disposed of; food and milk are handled under clean conditions; and a pure water supply is assured.

Although diarrhœa is a common symptom, it differs in type in the various diseases. Thus in typhoid fever the main incidence of the disease is upon the ileum, and the stools are typically of the pea-soup type. Dysentery particularly affects the large intestine, and the passage of blood and mucus with tenesmus and tormina are typical features. In cholera the small intestine is mainly involved and the stools are thin and watery.

It is sometimes convenient in a case of diarrhœa to describe the stools as being of the enteric, dysenteric or choleraic type. The main differences between them are set out in Table XXII.

Control of Ingestion Diseases.—The general measures outlined in Chapter IX, p. 73, are applicable to ingestion diseases. In the following summary those measures which are of particular importance are considered in more detail :—

A. PREVENTIVE MEASURES.

1. Sanitary disposal of human excreta.
2. Preparation of pure food and drink :—

   (i) *Water*—Purification of supplies.
   (ii) *Milk*—Healthy herds; hygienic milking; pasteurisation or other methods of subsequent purification.
   (iii) *Food*—Supervision of preparation, particularly of those foods which are moist and eaten raw, *e.g.*, shellfish, watercress.

3. Protection of food and drink against subsequent contamination by :—

   (i) *Humans*—Exclusion of carriers: persons known to be carriers should be excluded from handling food and milk; workers in public water works should be examined to exclude carriers.

   Personal hygiene of food handlers, who should adopt a rigid routine of hand-washing, particularly after using the toilet.

TABLE XXII

TYPICAL STOOLS IN ACUTE INTESTINAL INFECTIONS

	Enteric Fever	Bacillary Dysentery	Asiatic Cholera	Infectious Enteritis of Children
Size of stool	Large.	SMALL	LARGE (copious, abundant)	Usually small.
Consistency	Fluid (thick soup)	Fluid	WATERY	Fluid.
Colour	Yellow ochre or khaki "PEA SOUP"	Yellowish-white ± red (blood)	Milky-white "RICE-WATER"	Varies: GREEN, brown, orange or watery.
Odour	Offensive	Offensive	ODOURLESS	Offensive (sometimes odourless).
Fæcal matter	PRESENT	Little or none	ABSENT	Little or none.
Mucus	Nil	PRESENT ± PUS	Nil	Sometimes (± curds).
Blood	Slight or nil, unless complicated by hæmorrhage	PRESENT	Nil	Rarely present.
Number of stools	Few or many (3 to 20)	VERY FREQUENT (20 or more) except Sonne	VERY FREQUENT	FREQUENT (5 to 10).
Defæcation	Painless	PAINFUL, TENESMUS, TORMINA	Painless	Sometimes painful.
Organisms present	Typhoid or paratyphoid bacilli	B. dysenteriæ	Cholera vibrio	Nil.

The most characteristic features are printed in capitals, but are not necessarily constant.

(ii) *Flies*—Prevention of breeding; all food and milk should be screened if flies are prevalent.

(iii) *Rodents*—Extermination.

4. Active immunisation of the susceptible population if prophylactics are available.

B. MEASURES DIRECTED TO THE PATIENTS AND THEIR ENVIRONMENT.

1. Recognition of the disease, notification and isolation.
2. Concurrent disinfection of excreta.
3. Rigid personal hygiene of attendants, particularly washing of the hands after dealing with patients' excreta or fomites. In children's hospitals, special staff for feeding, who should not deal with excreta.

SUMMARY OF CHAPTER XXVII

Ingestion diseases include the acute alimentary infections caused by (i) specific organisms, (ii) unknown organisms or (iii) organisms of uncertain pathogenesis.

Importance of the non-lactose fermenting organisms of (i) the *Salmonella* sub-group and (ii) the *Dysentery* sub-group.

The mode of infection in all is by ingestion. Diarrhœa is common to all, but the character of the stools varies in enteric fever, dysentery, cholera and the infectious enteritis of children (Table XXII).

Measures of control, chiefly prevention of bowel-to-mouth infection by sanitary disposal of excreta and provision of pure food and drink.

CHAPTER XXVIII

INFECTIOUS ENTERITIS OF CHILDREN

ACUTE enteritis or gastro-enteritis of children is an infection or intoxication of acute onset characterised by an alimentary derangement in which diarrhœa is the most constant symptom, and vomiting and constitutional disturbances are common accompaniments.

Ætiology.—Many ætiological agents are capable of producing an acute diarrhœal disorder in infants, and in the present state of our knowledge it is impossible to separate the various types. In order to explain the position of infectious enteritis some classification of the diarrhœa is desirable, and the following, based on causation, is useful for clinical purposes :—

CAUSES OF ACUTE DIARRHŒA IN CHILDREN.

1. *Enteral causes, i.e.,* causes in the alimentary canal—*primary* diarrhœa.
   - (*a*) Infections with known specific organisms, *e.g., Bact. typhi, Bact. paratyphi, Dysentery bacilli, Bact. typhi-murium.*
   - (*b*) Infections with organisms of doubtful pathogenicity, *e.g., Proteus morgani, Paracolon bacilli,* etc.
   - (*c*) Infections with unknown organisms.
   - (*d*) Diarrhœa due to digestive disorders.
2. *Parenteral causes, i.e.,* causes outside the alimentary canal—*secondary* diarrhœa, *e.g.,* infections of the upper respiratory tract, otitis media, pyelitis, etc.

The enteritis described in this chapter concerns only primary enteral infections of unknown or uncertain causation. It is therefore a mixed group, with no definite clinical differentiation between its members. In a majority of cases of infectious enteritis no specific organisms can be isolated. In clinically similar cases *Proteus morgani, Paracolon bacilli* and other organisms are found, and the clinician is in doubt as to whether they are causal or are normal inhabitants of the alimentary

canal which have multiplied as the result of the pathological process in the intestines.

PREVALENCE AND PREDISPOSING FACTORS.—The most striking feature of the age incidence of enteritis is the peculiar susceptibility of children under two years of age. Infantile immunity is unknown in this disease. Outbreaks prevail among newborn infants, but the period of greatest susceptibility is between the ages of three and twelve months.

Equally striking is the almost complete "escape" of infants who are breast fed. Breast milk is not liable to the bacterial contamination of cow's milk. When the infant is taken off the breast and is introduced to cow's milk he is exposed to a variety of infective and toxic agents, some of which may be responsible for enteritis. This, together with the susceptibility of the infant, explains the age incidence of the disease. Breast feeding does not provide protection, it merely eliminates exposure to infection. Moreover, the exposure occurs at a time when the infant's alimentary canal and digestive processes are attempting to adapt themselves to artificial feeding. If there is any dyspeptic disorder, due to qualitative or quantitative errors of diet, enteritis is more likely to occur.

Although enteritis affects children of all social classes, it is more prevalent where there is poverty, overcrowding and uncleanliness. It is endemic in cities, and the incidence is higher in the poorer quarters. Outbreaks are liable to occur where children of a susceptible age are congregated together, as in children's hospitals or wards, nurseries, crêches, etc. Rickets, malnutrition, respiratory infections and any condition which lowers the resistance of the infant increases the liability to enteritis.

Formerly there was a marked seasonal increase in enteritis in the summer months, but this has largely disappeared.

MODES OF TRANSMISSION.—*Milk* is the most likely article of diet responsible for the conveyance of the infection, but the manner in which it is infected is uncertain. It may be contaminated at any stage from the cow to the infant's mouth, by those handling the milk or those preparing it for the child.

Although secondary diarrhœas are not considered here, it is interesting to note that when the infection responsible for diarrhœa is of parenteral origin, the mode of transmission is that of the primary infection, *e.g.*, upper respiratory tract infections are transmitted by droplets, and if such infections produce diarrhœa then the mode of spread is by droplets. The evidence on this point is, however, unconfirmed (*vide infra* Differential Diagnosis).

Clinical Manifestations.—The chief clinical manifestations are *diarrhœa*, *vomiting* and *dehydration*. Diarrhœa is the most constant symptom. Vomiting occurs if the stomach is also involved, *i.e.*, the condition is gastro-enteritis, which is commoner in the younger age groups and adds considerably to the seriousness of the disease. Dehydration, excessive loss of fluids due to diarrhœa and vomiting, only occurs in severe cases and is of serious prognostic significance as a profound toxæmic state is associated with it.

In severity the disease varies from a trivial attack with a few loose stools to a severe attack with persistent and intractable vomiting and dehydration. The onset may be gradual or sudden. In the mild cases there is little or no general disturbance, the only manifestation being an abnormality of the stools. They become loose and their colour changes to green ; fæcal matter is present and is sometimes admixed with mucus and curds ; the number of evacuations increases but rarely exceeds four a day ; frequently the stools develop an offensive odour. Because of the relatively slight general disturbance the condition may be overlooked. As the disease advances, constitutional disturbances appear but are rarely severe. They consist in slight pyrexia, loss of appetite, fretfulness, sleeplessness, failure to gain weight or actual loss of weight, poor muscle tone and loss of muscular vigour. This mild type of enteritis may persist for a few days only or continue for a week or two. Sometimes the course of the disease is protracted and temporary improvements are succeeded by periods of relapse, particularly if the diet prescribed is not suitable. Occasionally an inadequate diet may be responsible for the persistence of the symptoms.

Although cases of gradual onset may develop into severe attacks, usually those of abrupt onset are the most severe. In such cases the diarrhœa is associated with vomiting and considerable constitutional disturbance. The temperature rises rapidly to 103° to 104° and the child is obviously toxic. The stools rapidly become loose, profuse and frequent. Their colour may be green, brown, orange or, in the worst cases, watery. Fæcal matter may entirely disappear and the diarrhœa become uncontrollable. The odour is offensive, but if the stools become watery and alkaline the unpleasant odour disappears. Vomiting soon sets in, and may become so intractable that everything taken by mouth, even water, is returned. There is rapid loss of weight, and if the condition advances, signs of water loss and intoxication appear.

Severe dehydration (exsiccosis) manifests itself clinically by

loss of turgor or fullness of the tissues, *e.g.*, the shrinking of the subcutaneous tissues, rapid loss of weight, insatiable thirst and oliguria. The scanty urine, of high specific gravity, sometimes contains albumen and casts.

In the worst cases the cheeks are pinched, the eyes are sunken; the skin is wrinkled and inelastic, so that it fails to return rapidly to its normal position when pinched up; the bony prominences become accentuated and the anterior fontanelle depressed.

In enteritis the toxæmia produces an increased permeability of cell membranes and the diarrhœa results in considerable loss of fluids. Thus there is considerable disturbance in water balance.

Water constitutes a high percentage of the body-weight of the infant, and all the essential biochemical reactions take place in this fluid. The changes in water balance disturb the general metabolism and interfere particularly with the excretion of waste products, the assimilation of food, the building up of the tissues, the maintenance of the blood volume and the regulations of the temperature. If water balance is seriously disturbed, tissue cells break down to form water and acid metabolytes. The latter increase the necessity for water and thus a vicious cycle is set up and *acidosis* is liable to supervene. This situation is aggravated by a number of subsidiary factors. The diarrhœa results in loss of base (*i.e.*, sodium salts) in the stools, thus depleting the alkali reserve. The diseased and rapidly emptying intestinal tract fails to absorb food and semi-starvation follows. In consequence, the tissue cells break down and ketone bodies are formed (oxybutyric acid, aceto-acetic acid and acetone). Lastly, the toxæmia increases tissue breakdown with the production of acid metabolytes. Thus dehydration, toxæmia and acidosis continue and produce a fatal issue unless the water loss can be overcome. If it is not, the more serious manifestations appear. There may be nervous symptoms—restlessness, irritability, convulsions, apathy, stupor or semi-consciousness; the heat regulation may be disturbed, so that there may be hyperpyrexia; or the patient may pass into a state of collapse with normal or subnormal temperature; the shrunken and pinched infant lies in a semi-conscious state, half-opened eyes are dulled by a mucous film, the extremities are cold, the breathing irregular and the pulse feeble. If ketosis is marked the respirations may be deep and the breath smell of acetone. Recovery from this stage of the disease is unusual.

If there has been much vomiting, the loss of chlorides in the vomitus may produce an *alkalosis* instead of the *acidosis*

which occurs in cases with severe diarrhœa. Clinically, it may be extremely difficult to decide which is present. Biochemical tests to assist the clinician are attended with considerable practical difficulties.

Case Fatality Rate.—The younger the child, the more likely is the disease to be severe and the greater the fatality. Among newborn infants rates of 70 per cent. are recorded. Generally the percentage of deaths in severe outbreaks is 40 to 60 per cent. and in mild ones 20 to 30 per cent. In infants much below weight from malnutrition or other diseases, enteritis is almost always fatal. After two years of age deaths are much less common and the disease does not give rise to the anxiety which it does in infants.

Differential Diagnosis.

1. OTHER ACUTE DIARRHŒAL DISORDERS.—The differentiation of enteritis or gastro-enteritis from other acute diarrhœal disorders is often difficult and sometimes impossible.

(*a*) *Infections due to known specific pathogens* usually produce typical syndromes, *e.g.*, dysentery is an enterocolitis with blood and mucus in the stools; enteric fever is a toxæmia with pea-soup stools. But in infants it sometimes happens that, instead of these typical features, the disease manifests itself as an ordinary attack of enteritis or gastro-enteritis. Sonne dysentery and paratyphoid fever may behave in this way. It is therefore necessary, in every case of diarrhœa in children, to exclude the specific diarrhœas. Bacteriological examination of the stools should always be carried out; but unfortunately the specific organisms often disappear rapidly from the stools, and a negative result does not exclude the disease with certainty. The development of specific antibodies sometimes permits a retrospective diagnosis to be made, but even then it is not certain.

(*b*) *Secondary diarrhœa* due to some parenteral infection must be excluded, as in such cases the primary disease requires attention or the diarrhœa will persist. The commonest causes are upper respiratory tract infections, such as the common cold, otitis media, measles, whooping-cough and pneumonia.

It must not be supposed that the diarrhœa which complicates such infectious diseases as measles, whooping-cough and influenza are all examples of

parenteral infections. The diarrhœa may be due to the same organism which produces the respiratory infection invading the alimentary canal; or it may be truly parenteral, *i.e.*, at the site of the respiratory infection *toxins* are elaborated which act upon the bowel; or the lowered state of the patient may permit the activation of intestinal organisms which are normally non-pathogenic; or, lastly, it may not be a secondary diarrhœa at all, but a primary one, due to a superimposed enteral infection. In the present state of our knowledge differentiation is impossible; since many such cases behave as if the diarrhœa were a second infection, it is wiser to treat them all as if this were the case.

(*c*) *Dyspepsias* should only be diagnosed after the infections, both enteral and parenteral, have been excluded.

(*d*) *Food Infections and Poisonings.*—Acute enteritis in children is strictly a form of food infection, but is not usually classified as such. The food infections and poisonings are due to a variety of organisms, most often to certain members of the Salmonella group, such as *Bact. typhi-murium*, or to staphylococci, or to organic or inorganic poisons present in the food or produced there as the result of the presence of bacteria. The condition is not restricted to children, and is commonest in adults taking meals away from home in restaurants and eating-houses. The symptoms may develop one to twenty-four hours after the ingestion of the food, and take the form of acute enteritis or gastro-enteritis with diarrhœa, vomiting, prostration, headache and pyrexia. Examination of food, stools and vomitus is necessary to determine the cause, as a variety of ætiological agents may be responsible.

2. ACUTE INFECTIONS.—If the diarrhœa passes unnoticed, the general disturbance may be thought to herald the onset of a number of possible diseases. An inquiry should always be made into the state of the stools in children under two years of age.

3. PNEUMONIA.—Enteritis may complicate pneumonia or be mistaken for pneumonia. Infectious diseases such as measles and whooping-cough may be complicated by both broncho-pneumonia and enteritis, but the obvious respiratory involvement may divert attention from the enteritis, although the

latter may contribute considerably to the gravity of the illness.

4. MENINGITIS. — The nervous manifestations in severe enteritis simulate an intracranial infection, but the examination of the cerebrospinal fluid will settle the diagnosis. *Per contra*, meningococcal meningitis may be missed because attention is focused on a secondary diarrhœa.

5. INTUSSUSCEPTION is commonest in boys under one year. Typically the stools contain blood and mucus, and no fæcal matter is passed. A tumour may be palpable, and the right iliac fossa empty.

Treatment.

GENERAL MANAGEMENT IN HOSPITAL.—Since various agents are responsible for enteritis, and most cases exhibit features of a dangerous infectious disease, every case must be treated as a separate entity. This implies nursing each patient separately, either in an isolation ward or by barrier nursing. The nursing of infants with enteritis demands considerable time and experience. In hospitals a dual staff of nurses should be provided, the "feeders" to prepare feeds, feed the infants and attend to the hygiene of the mouth; and "changers" to change infants, sluice linen or squares and take rectal swabs. Accurate early weighing of infants with enteritis is as important as the taking of the temperature.

Care must be taken in the disposal of infected linen. For children under six months destructible squares are convenient. Ordinary squares should be received into a receptacle containing 2 per cent. lysol. Equally important are the measures which must be taken to ensure clean feeds. Care is necessary not only in the handling of food but in its preparation. Bottles and teats should be sterilised; milk should be pasteurised or boiled and water should be boiled before use. Unless there are very strong reasons to the contrary, children who are breast fed should not be admitted to hospital. If they are, the mother should attend to feed the infant as soon as it is fit to resume breast feeding. The quantity of fluids or food taken, the number of stools and their character should be recorded daily.

THERAPEUTIC MEASURES.—However classified, the treatment of acute diarrhœa of all forms is carried out along the same lines. Two measures are invariably employed :—

(i) *Rest*, particularly rest of the alimentary canal by starvation and special feeds.

(ii) Measures designed to correct the *disturbed metabolism*, particularly the administration of fluids and salts.

Various *optional* measures are sometimes employed :—

(i) Emptying the alimentary canal of its toxic contents by stomach wash-outs, colon wash-outs and the exhibition of purgatives such as castor oil, mercurials, rhubarb and milk of magnesia.

(ii) The administration of intestinal antiseptics and detoxicating agents. The commonest in use are salol, mercurials, certain dyes and kaolin, but they are of doubtful efficacy.

(iii) The administration of intestinal sedatives, such as bismuth, chalk and opium. Many pediatrists consider them dangerous, as they are said to permit the retention of toxic intestinal contents. Opium, if exhibited at all, should be given in very small doses only after the alimentary canal has been emptied. Astringents such as tannic acid, tea and silver nitrate are also employed. The scope for the use of drugs in enteritis is not wide.

(iv) Miscellaneous measures, such as the exhibition of stimulants and the giving of blood transfusions.

The multiplicity of therapeutic measures is a sure indication of the inadequacy of all of them. The following scheme is as successful as most :—

Rest and conservation of energy are essential in the severe diarrhœas. The application of this principle may, in certain cases, contraindicate the employment of measures likely to disturb the infant, such as wash-outs, transfusions, infusions, etc. The patient must be kept under the best hygienic conditions and requires frequent attention. The room should be light, well ventilated and warm, and care should be taken to maintain the body temperature.

Unless the patient is collapsed, treatment should begin by clearing the alimentary canal. A single dose of castor oil, followed next morning by a colon wash, can be given to most cases. If vomiting is present, a stomach wash-out before the administration of the oil may permit the purgative to be retained.

Rest of the alimentary canal is secured by starving the patient for the first twelve to forty-eight hours. It should not be prolonged longer than necessary, as infants with enteritis bear starvation badly. During this time fluids should be given as outlined below. After this, relative rest of the alimentary canal and the provision of energy is secured by the prescription of an easily digested, easily assimilable, non-residue-forming and non-irritating diet. Many prescriptions are available,

indicating the difficulty in ordering a successful diet in individual cases. Milk is usually unsuitable in unmodified form. The digestive difficulty may involve all the constituents of the milk, but fats and proteins usually require to be drastically reduced. The protein is said to aid the infective process in the bowel and this is another reason for its reduction. Generally whey followed by a half-cream dried milk or a skimmed milk carry the infant over until a more liberal diet can be resumed. Throughout the treatment the caloric requirements of the child should be known from its age and weight and the caloric content of the diet estimated and charted. It is not to be anticipated that the full caloric requirements can be met in the early treatment of the acute stage, but a diet which is producing semi-starvation cannot be prolonged unduly without danger. Occasionally unorthodox diets such as raw banana and raw or dried apple (20 to 30 gm. for one to three days) are successful.

The administration of fluids and the correction of the disturbed metabolism are fundamental measures in all cases of enteritis. They should not be delayed until signs of dehydration appear, as by then this is difficult or impossible to overcome. Fluids should be introduced by the easiest possible route so as to disturb the patient as little as possible. If necessary, every possible route must be tried and oral, rectal, subcutaneous, intraperitoneal and intravenous administration are all practised. For intravenous injection any available vein should be used—the antecubital, external jugular, femoral or superficial temporal—or the superior longitudinal sinus. For continuous intravenous administration of fluids by the drip method, a vein near the ankle is usually employed. In acute dehydration it may be necessary to administer as much as 1000 c.c. of fluid a day. Even if it is successfully introduced. the changes in permeability may prevent its proper utilisation by the tissues. In diarrhœa, salts are lost, and the store of glycogen in the liver is rapidly exhausted. In practice, the commonest procedure is to add sodium chloride (to make an isotonic solution) and glucose (5 to 10 per cent.) to the fluid to be administered. The simplest method of giving fluids, and one which is often very successful, is to give half-strength saline by mouth. Other substances used for salt replacement are sodium bicarbonate, Ringer's solution (containing sodium, potassium, calcium and chloride) and Hartmann's physiological buffered salt solution, with or without the addition of 5 to 10 per cent. glucose. Most of the chemicals used not only replace salt but also increase the alkali reserve.

In addition to the diminution of salts, there is also deficiency of acid in the upper part of the small intestine, due in part to vomiting and in part to the diminution of gastric secretion from toxæmia and pyrexia. In consequence, intestinal organisms can grow at a higher level than normal in the alimentary canal, and some importance has been attached to this fact. Hartmann's method of overcoming this abnormality is to administer lactic acid buffered with sodium lactate. It serves two purposes: the lactic acid inhibits bacterial growth by acidifying the upper intestinal tract, and sodium lactate provides base to overcome the toxæmia.

Blood transfusion has been tried in recent years for gastro-enteritis. Because of the anhydræmia and the unavoidable slowing of the circulation, it should not be tried until full fluid restoration has been accomplished.

Despite the many measures available, the treatment of severe cases of enteritis is very unsatisfactory and it is doubtful if the fatality rate can be materially influenced.

SUMMARY OF CHAPTER XXVIII

Causes of Acute Diarrhœa in Children :—

1. *Enteral :* (*a*) *infections* with known and unknown organisms and with organisms of doubtful pathogenicity.
   (*b*) *digestive disorders.*
2. *Parenteral Infections.*

INFECTIOUS ENTERITIS.

Mode of Transmission : Probably ingestion.

Clinical Manifestations : Diarrhœa, vomiting and dehydration.

Treatment :

(i) Preliminary starvation followed by relative alimentary rest.

(ii) Exhibition of fluids.

CHAPTER XXIX

DYSENTERY

DEFINITION.—A colitis or ileocolitis, usually with ulceration, characterised by diarrhœa with the passage of blood and mucus or mucopus, and accompanied by colic and discomfort on defæcation. Two types of dysentery occur :—

(i) *Bacillary dysentery*, due to an infection with dysentery organisms, of which the following are the most important :—

(*a*) *Bact. shigæ.*

(*b*) *Bact. flexneri*—of which there are several strains.

(*c*) *Bact. sonnei.*

(ii) *Amœbiasis*, or amœbic dysentery, due to an infection with *entamœba histolytica.*

I. BACILLARY DYSENTERY

Ætiology.—*Prevalence.*—Like all other enteral infections, dysentery is most prevalent where hygiene is poor and sanitation defective. It is mainly a disease of sub-tropical and tropical countries. In temperate zones, where, as a rule, greater care is taken in the disposal of sewage and in the provision of clean water, milk and food, dysentery is usually sporadic. It was not always so. Formerly it was a serious epidemic disease and it was responsible for many deaths. It was particularly prevalent in armies in the field provided with primitive sanitation, and was often endemic in prisons, asylums, hospitals and camps. Although it is becoming less common in this country, outbreaks still occur, particularly in institutions. In children's hospitals outbreaks are now usually due to the Sonne strain and in asylums to Flexner or Sonne strains. Both these strains are found in sporadic cases, but Shiga infections are almost unknown in Great Britain.

Mode of Transmission.—The source of dysenteric infections is polluted water, milk or food. Infection of water may result from direct contamination by excreta. Food and milk may be

infected by those handling it if they are carriers, or attendants, or patients suffering from dysentery. Flies have long been regarded as important agents in its spread, the organisms being carried on the feet from excreta to food; but sometimes dysentery bacilli are carried for a few days in the insect's intestinal tract. When the fly feeds it also defæcates, thus contaminating food on which it alights (see Ingestion Diseases, Chapter XXVII).

Clinical Features.—Following the ingestion of the infected food or drink, an incubation period of two to seven days occurs. The disease is usually abrupt in onset, but the acme is not reached for two to four days. Sometimes it starts insidiously. All gradations of severity occur, from mild cases with transient diarrhœa to severe cases with discharging, almost incessant, diarrhœa, and severe general disturbances which may prove fatal. There is a definite correlation between the type of dysentery bacillus and the severity of the disease. Shiga infections are much the most severe and are often associated with severe toxæmia which does not occur with Flexner and Sonne infections. Complications are almost invariably associated with Shiga infections.

In the worst cases the three typical symptoms—colic, diarrhœa and discomfort on defæcation—are most distressing. The colic consists in frequent spasms of clutching or griping abdominal pain which start gradually, rapidly increase in intensity and then wane. There is a more or less constant sensation of weight in the rectum, and a frequent, sometimes incessant, desire to defæcate. On going to stool, sometimes nothing is passed. The passage of a stool is associated with straining, and if the lower part of the rectum is affected there is a burning pain in the rectum and anus. Defæcation provides little or no relief from the colic and rectal sensations. At the beginning the number of stools passed in twenty-four hours may be four or five, but in the course of the first day or two the number may rise suddenly. Generally, some ten to forty are passed, but in the most severe cases the number may reach the extraordinary figure of two hundred. During the first day or so the stools may be merely loose and yellowish-brown, or even scybalous with a little mucus and blood; but when the diarrhœa is established the stools acquire the typical dysenteric characters. They are small, sometimes very small; fæcal matter is absent and the stools consist entirely of bloody, gelatinous mucus or mucopus floating in a little serum. At the beginning the blood consists of streaks or small lumps; later large clots or even pure blood may be passed. In the

most severe cases shreds of mucosa may be present and the rectal discharge may appear black, offensive and gangrenous. On examination of the abdomen the large bowel may be found spastic and tender.

Vomiting is not a common symptom of dysentery ; it may occur at the onset and may appear later in the disease in severe cases.

The general symptoms are due to toxæmia from the infection and prostration from the diarrhœa. There is moderate pyrexia (101° to 103° F.) with headache, malaise, anorexia and a dirty tongue. As the diarrhœa advances there is great thirst, loss of weight, dizziness, dry sallow skin, weakness and prostration.

In those cases that recover, improvement begins after about a week. The symptoms abate gradually. The stools diminish in frequency and mucus becomes opaque, the amount of blood decreases, fæcal matter reappears and increases in quality, and the stool gradually acquires consistency until a formed motion is passed. If recovery does not occur, exhaustion becomes more marked, wasting and weakness increase, the face becomes pinched, the extremities livid and cold, the voice hoarse, the pulse rapid and imperceptible, and the patient dies of exhaustion and toxæmia.

At the other end of the scale of clinical severity is the mild enterocolitis which characteristically occurs as the result of Sonne infection in children. The general disturbance is slight, the temperature seldom rising above 100° to 101° F. The diarrhœa is not pronounced, there being seldom more than four or five stools a day. The motions are loose, and some fæcal matter usually remains. Mucus and blood are characteristically present. Colic and rectal symptoms are slight or absent, but there is often a little tenderness over the descending colon. In children, more severe cases may be associated with vomiting. In the mildest cases the only symptoms are a few loose stools, which in children are often green, with mucus and little or no blood.

Generally the condition clears up in a few days and rarely causes death. Compared with enteritis or gastro-enteritis, with which it is sometimes confused in children, Sonne dysentery is a relatively trivial disease.

Complications and Sequelæ.—Complications are not common and are almost always the result of Shiga infections. A local peritonitis may occur, *e.g.*, around the descending colon or rectum. Scarring of the healed mucosa or at the site of the local peritonitis may result in stricture and obstruction. In

chronic cases a polyposis of the large bowel may supervene. Other complications are irido-cyclitis, corneal ulceration, neuritis (which may result in paralysis of a limb or paraplegia), arthritis, often monarticular, which may appear after the acute symptoms have subsided, and, more rarely, pyæmia and inflammation of serous linings such as pleurisy, pericarditis and endocarditis. Recovery from Shiga infections is often a slow process, and patients may remain weak and debilitated for months. This prolonged invalidity may be associated with an irritable intestinal tract, so that the patient may be readily subject to dyspepsia and diarrhœa.

Convalescent carriers of dysentery bacilli are not uncommon (see p. 350).

Chronic bacillary dysentery usually follows on an acute attack, and is more likely to occur after Shiga infections. The patient becomes progressively thinner, weaker and more anæmic. Colic and rectal symptoms are usually absent, except in the acute exacerbations which occur from time to time. Diarrhœa is not nearly so marked, *e.g.*, four to six stools in the twenty-four hours. In consistency the stools vary from a soft, formed, almost normal motion to a loose stool mixed with a certain amount of mucus and pus and occasionally a little blood. Sometimes constipation alternates with diarrhœa. Any dietetic indiscretion, or attempt at work, may precipitate a relapse. Recovery may occur, or the patient may die of exhaustion, a complication, or an intercurrent infection.

Aids to Diagnosis.

Clinical Aids.—Examination of the rectum and colon by a proctoscope or sigmoidoscope may show changes in the mucosa which assist in making the diagnosis in doubtful cases. There may be simple catarrhal inflammation or actual ulceration. These examinations are, however, most important for the exclusion of other diseases, such as carcinoma of the bowel, polyposis and ulcerative colitis, and for watching the progress of chronic cases of dysentery.

Bacteriological Aids. In every case of dysentery bacteriological examination of the stools should be carried out to confirm the diagnosis. In doubtful cases the isolation of the organism may clinch the diagnosis. Unfortunately, in many cases of dysentery the organism disappears rapidly from the stools. The most successful results are obtained if the examination is carried out in the first two or three days on the bloody mucopus in the stools. If the specimen cannot be transmitted to the laboratory for immediate examination, steps

should be taken to preserve it in glycerol and saline, as the specific organism may die off rapidly. Instead of a specimen of fæces, or of the mucopus which forms the stool, a rectal swab may be sent. In the less acute cases a swab of an ulcer taken through a sigmoidoscope may provide a more satisfactory specimen for bacteriological examination than the fæces themselves.

Serological Aids.—The isolation of the specific organism from the stools is a more satisfactory test than the detection of antibodies in the blood. Agglutinins, which are the antibodies tested for, do not appear in the blood until the second week of the disease (seven to fourteen days). The interpretation of results is difficult because normal blood serum is sometimes capable of agglutinating dysentery bacilli and cross agglutination between strains occurs.

Agglutination reactions which may be considered suggestive are :—

Bact. shigæ	$\frac{1}{40}$
Bact. flexneii	$\frac{1}{150}$
Bact. sonnei	$\frac{1}{100}$

Sometimes in a definite infection with dysentery bacilli, agglutination does not occur in these dilutions and occasionally it cannot be detected at all. Usually agglutinins diminish shortly after convalescence and may be absent after three months. A rising titre in the second week of the disease, followed by a decline after convalescence, is of much more diagnostic value than the result of a single examination, but diagnosis is thereby delayed.

Differential Diagnosis.—Typical cases of dysentery present no difficulty. Although there are points of difference in the clinical features of *bacillary* and *amœbic* dysentery, their ultimate differentiation depends upon the examination of the stools. Other diarrhœal disorders such as *food poisoning* and *enteric fever* may require to be differentiated (see pp. 340, 379). Under war conditions dysentery and enteric fever sometimes occur together and one may mask the other. In such cases diagnosis depends upon bacteriological and serological tests. In atypical cases of dysentery, abdominal conditions such as *appendicitis, peptic ulcer, cholecystitis* and *pancreatic disorders* may be confused with the disease. In chronic cases *carcinoma of the bowel* and *ulcerative colitis of non-dysenteric origin* must be excluded. When arthritis and neuritis complicate the picture the diagnosis may be further confused.

In children the two conditions which are most commonly

confused with dysenteric ileocolitis are *enteritis* and *intussusception*. In enteritis the passage of blood is unusual and the organism is absent from the stools. The age of children suffering from ileocolitis is usually greater than those with enteritis and intussusception. Over two years of age intussusception is rare ; it is commonest in boys under a year. The passage of blood and mucus is associated with obstruction to the bowel, no fæces being passed. A tumour may be palpable, and the right iliac fossa is "empty." In ileocolitis the blood and mucus are associated with diarrhœa. Some fæcal matter is usually present in the stools, and the descending colon may be spastic and slightly tender.

Treatment.—The principal lines of treatment for bacillary dysentery are rest, diet, the administration of anti-serum and symptomatic treatment.

The patient should be kept in bed, and in severe cases rest should be absolute. An initial purgative is usually given (sodium sulphate or castor oil) and this may be continued in small doses throughout the illness.

At the beginning a period of starvation is imposed, even milk being withheld in some cases. Fluids with glucose (5 to 10 per cent.) are given *ad libitum*. Thereafter the diet is gradually increased, care being taken to exclude irritating, residue-forming articles. A raw apple diet or apple porridge has also been used.

The therapeutic serum usually used is a polyvalent, *antibacterial* serum prepared by injecting horses with vaccines and living cultures of Shiga and strains of Flexner bacilli. An *antitoxic* serum prepared by injecting the toxin of Shiga organisms is available for use in this type of the disease. Serum should be given as early as possible, preferably intravenously in a single dose of 60 to 100 c.c. Serum therapy is not necessary for the mild infections with Sonne's bacillus.

Of symptomatic treatment, the most valuable is heat to the abdomen by means of electric pads, hot strips, poultices or hot bottles. For tenesmus, starch enemata should be given. Opium may be given occasionally to ensure that the patient receives rest.

For Shiga infections sodium thiocyanate intravenously is said to be of value. It is given in the first twenty-four hours intravenously, 20 mgm. per kg. of body-weight, and the daily dose not to exceed 1 gm. If it is not speedily successful it may be repeated for three days.

Bacillary Dysentery Carriers.—Carriers of dysentery bacilli are invariably intestinal carriers, the organism being passed

in the fæces, and such carriers are formed among those who have recovered from the disease and those who have never had it—convalescent and contact carrier. In some of them organisms are constantly present in the fæces—persistent carriers. In others they are found intermittently and may therefore be missed on one examination only. This intermittency may be very marked. The patient may pass the organism for a day or two, and then be clear for a month or more. Sometimes convalescent carriers are transient carriers, *i.e.*, the organism persists for a short time after convalescence is established and then disappears. Occasionally the organism cannot be detected at all, and the diagnosis of the carrier state is arrived at by circumstantial evidence, *e.g.*, an outbreak of dysentery occurs in a ward ; all patients except one suffer from diarrhœa ; in the unaffected patient no dysentery bacilli can be detected, but the blood contains agglutinins in high titre ; it is a reasonable inference that this one is the probable cause of the outbreak.

Dysentery carriers may be asymptomatic or may suffer from ill-health and attacks of diarrhœa. This difference is often associated with the type of organism carried. Shiga carriers often look ill, are liable to intestinal upsets and diarrhœa, and tend to carry the organism persistently. Flexner and Sonne carriers are often healthy and the more likely to carry intermittently.

In searching for carriers, routine bacteriological examination is often not enough because of the intermittency of the carrier state. Sometimes provocative doses of vaccine are given, but dysentery vaccines are inclined to produce unpleasant reactions. If they are used they may stimulate the bowel to excrete the organism. The stools are examined for mucus, blood and pus, and plated out for organisms. A saline purgative may also be used for the same purpose. The blood is also examined for agglutinins, but the limited value of the procedure has already been noted.

II. AMŒBIASIS

(AMŒBIC DYSENTERY)

Definition.—*Amœbiasis* is due to the ingestion of a unicellular parasite, the *Entamœba histolytica*. Amœbic *dysentery* is the commonest part of the clinical picture, but *hepatitis* and *liver abscess* are common complications, particularly in untreated cases.

Ætiology.—Although most prevalent as an endemic disease of tropical and subtropical countries, war conditions, *e.g.*,

transfer of troops, insanitary disposal of excreta and primitive methods of water purification, may result in its introduction into temperate zones. Kagy (1939) maintains that the organism is widespread throughout the world, a percentage of carriers existing in temperate zones.

Water polluted by infected fæces is the commonest source of infection, hence the prophylactic importance of safe drinking water, especially for troops in endemic areas. Food grown on soils manured by infected excreta is also important, but dissemination by flies and food handlers is not of frequent occurrence.

Pathology.—The *Entamœba histolytica* is present in walls of the intestinal ulcers, the fæces and the pus and walls of liver abscesses. The *vegetative form* (trophozoites), found chiefly in the mucus passed in the acute phase, consists of a mobile amœba—a single-celled organism with a small, indefinite, eccentric nucleus. The protoplasm comprises a darker granular endoplasm around the nucleus and a transparent, amorphous ectoplasm with pseudopodia in which flowing movements of the protoplasm can be seen. Unless examination is made on a warm slide, these movements rapidly cease and the amœba dies. Red blood cells engulfed in the protoplasm are common. The *encysted* form is resistant, and is commonly the only form detectable in chronic or quiescent phases of the disease. Differentiation from *E. coli*, a harmless parasite, is most commonly necessary. The vegetative phase is difficult; the *E. coli* is more sluggish, the nucleus more distinct and vacuoles are present in the protoplasm, but no red blood cells. The cysts of *E. coli* contain eight nuclei, whereas that of *E. histolytica* contain only four.

The organism grows in the *submucosa* of the large bowel, particularly in the cæcum and ascending colon. The local inflammatory infiltration of the submucosa (chiefly with round cells) is followed by necrosis which involves a smaller area of the overlying mucosa. A "flask-shaped" ulcer is thus produced, the neck being the aperture in the mucosa, the edges of which are therefore overhanging and undermined. Spreading and confluence of individual ulcers may result in extensive sinuous tracks in the submucosa bridged by apparently normal mucosa. In severe acute cases infiltration and œdema are diffuse, the bowel is riddled with ulcers and covered with a gangrenous, cobweb-like mucosa.

Spread of amœbæ to the liver via the portal vein results in diffuse degenerative changes (*hepatitis*) or actual necrosis in small scattered areas, one or more of which may enlarge

and soften to form *abscesses*. A single abscess on the diaphragmatic surface of the right lobe is most common. At first the necrotic wall is ragged, the contents a thick, soft mass, the colour yellowish-grey, red or chocolate, depending upon the admixture of liver tissue and blood; amœbæ are present. When chronic, the abscess is encapsulated, the wall smooth and fibrous, the contents more fluid and amœbæ can be found only in the wall.

Incubation Period.—This is very variable, due in part to the indeterminate onset of symptoms. Whilst commonly three or four weeks, it may be as short as two days in severe infections and as long as three or four months in subacute or chronic cases.

Clinical Features.—Clinically the disease is characterised by an insidious onset, frequent febrile relapses and a tendency to chronicity, but cases with acute onset occur resembling bacillary dysentery or acute surgical conditions of the abdomen. Mild ambulant cases are of frequent occurrence and, with *carriers*, many of whom give no history of having suffered from the disease, constitute potent sources of dissemination.

Diarrhœa is the outstanding symptom, but it may be absent, particularly in mild cases, or may alternate with constipation. The stools may be merely soft or loose, but generally they are dysenteric, blood and mucus being admixed with fæces. Rarely in the most severe cases fæcal matter is absent, the frequent stools consisting entirely of pink mucus. Straining and tenesmus are less common than in bacillary dysentery because the sigmoid colon and rectum are less affected.

Other symptoms are variable, depending upon the acuteness of the attack. Pyrexia is usually slight or absent. In mild cases digestive disturbances, anorexia and a little abdominal discomfort are common; in severe cases considerable toxæmia may occur. There may be abdominal tenderness and the thickened bowel may be palpable, particularly in the right iliac fossa.

In *hepatitis* there is pain on the right side and under the costal margin sometimes referred to the right shoulder; the liver is enlarged and tender; there is persistent pyrexia, a polymorphonuclear leucocytosis and sometimes an icteric tinge. These manifestations may abate, the condition becoming chronic, debility, cachexia and a muddy complexion supervening; or the condition may be chronic from the onset. Although there is usually a history of recent or remote dysentery, sometimes it cannot be obtained. The condition is commoner

in Europeans, addiction to alcohol whilst in the tropics with consequent damage to the liver being regarded as predisposing factors. In *amœbic abscess* the signs of hepatitis are present and it may be difficult to decide that abscess formation has supervened. Suggestive signs are a recurrence of pyrexia, often intermittent, rigors, sweats, extension of the liver dullness upwards, an increasing tenderness of the organ and a failure to respond to treatment with emetine. Cough and pulmonary signs at the right base may be present and X-rays may reveal an elevated and immobile diaphragm with basal opacity from collapse. The abscess may rupture into the pleura, lung, peritoneum or abdominal viscus.

Aids to Diagnosis.—Examination of the stools for amœbæ and cysts, blood counts for the polymorphonuclear leucocytosis which is present in amœbiasis, and radiological examination for liver abscess are mentioned above. Stools should be examined as soon as passed, as amœbæ die rapidly. Several specimens should be examined, a single negative finding being insufficient to exclude the disease. Stools with few cells, chiefly mononuclear and with Charcot-Leyden crystals, are suggestive of the disease. Sigmoidoscopy may reveal small red ulcers with a hæmorrhagic margin on otherwise normal mucosa. In hepatitis, the lævulose tolerance test may show some hepatic deficiency. In endemic areas patients with unexplained pyrexia or a tender liver should be subjected to a *therapeutic test* with emetine.

Differential Diagnosis.—Every *diarrhœal disorder* in persons who have lived in endemic areas should be investigated by examination of the stools for amœbiasis. Differentiation from *bacillary dysentery* is important because treatment is entirely different. Acute cases may be confused with *acute surgical conditions of the abdomen*. Hepatic amœbiasis requires to be differentiated from *malaria*, *pneumonia*, *empyema*, *gallstones*, *suppurative hyatid cysts* and *renal infections*.

Prophylaxis.—The general measures outlined in Chapter XXVII, p. 332, are applicable to amœbiasis. Special attention is necessary to the sanitary disposal of excreta and the provision of a pure water supply. Systematic inspection to eliminate cross-connections between potable and polluted supplies are necessary. Dubious water should be boiled, chlorination being inadequate for the destruction of cysts. Raw vegetables should be avoided or washed in chlorinated water. Food should be screened from flies and food handlers supervised. Known carriers should be instructed in hygiene of the toilet and should be prohibited from handling food.

Treatment consists in rest, diet and one or more courses of emetine. In acute cases rest should be absolute. Diet should follow the lines indicated under bacillary dysentery (*vide* p. 350), but saline purgatives are contraindicated. *Emetine* is a very effective remedy, but must be given under close supervision as it is a cardiac depressant and a gastro-intestinal irritant. Even carriers should be kept in bed and the pulse watched. A course of treatment consists in :

(i) *Emetine hydrochloride,* twelve daily subcutaneous or intramuscular injections of 1 gr. in 1 c.c. of distilled water. The injections may be painful. This form of emetine acts chiefly on amœbæ in the gut wall and is most effective for the acute stage. It should be followed by

(ii) *Emetine-bismuth-iodide,* twelve daily doses of 3 gr. by mouth, which acts chiefly on parasites in the lumen of the bowel and is the most effective part of the course for chronic cases and carriers. This powder is a severe gastro-intestinal irritant causing nausea, vomiting and diarrhœa. It should be given in gelatine-coated capsules at night, after a meal, and the patient advised to struggle against any tendency to vomit. Tinct. Opii. ♏x̄ half an hour before the administration may be helpful.

Most early cases respond to emetine and the case fatality is low. Convalescence may be prolonged and relapses occur, although re-infection is sometimes responsible. Chronic cases and carriers tend to be more resistant and other drugs such as "Stovarsol" and "Yatren" are worth a trial. Freedom from infectivity is determined by repeated examination of the stools.

Liver abscess is treated by aspiration and emetine.

SUMMARY OF CHAPTER XXIX

I. BACILLARY DYSENTERY :—

Causal Agent : Bact. shigæ, flexneri, sonnei.

Symptoms : Diarrhœa, passage of blood and mucus, discomfort on defæcation.

Aids to Diagnosis : Sigmoidoscopy, bacteriological examination of stools, serological examination for antibodies.

Treatment : Chiefly symptomatic—serum available.

Prophylaxis : Elimination of carriers, pure food and water.

II. AMŒBIASIS (Amœbic dysentery) :—

Causal Agent: *Entamœba histolytica* (trophozoites and cysts).

Symptoms: Diarrhœa, passage of blood and mucus; liability to hepatitis and liver abscess. (More insidious than bacillary dysentery.)

Aids to Diagnosis: Microscopic examination of stools for parasites, blood count (polymorphonuclear leucocytosis), sigmoidoscopy.

Treatment: Emetine: course of twelve daily injections of emetine hydrochloride (gr. i) followed by twelve daily doses of emetine-bismuth-iodide (gr. iii).

Prophylaxis: Supervision of carriers, pure water supply.

CHAPTER XXX

ENTERIC FEVERS (TYPHOID AND PARATYPHOID)

DEFINITION.—Enteric fever, which includes typhoid and paratyphoid fever, is caused by the ingestion of fluid or solid articles of diet contaminated with the specific causal organisms (*Bact. typhi* and *Bact. paratyphi*). A long but variable incubation period is followed by an insidious invasion characterised by malaise, lassitude and vague abdominal discomfort. The temperature mounts progressively. This stage persists for about a week and then merges into one in which to the indefinite clinical picture of general toxæmia are added an eruption, splenomegaly and more definite signs and symptoms of intestinal localisation. The condition of the patient deteriorates, pyrexia being maintained at a high level with but slight morning remissions. After a variable number of days, the general toxæmia and local intestinal manifestations abate and the temperature falls to normal by slow lysis. Whilst at any save the earliest stage the patient is at risk from cardiac failure or pulmonary complications, the perils of local intestinal calamities, hæmorrhage or perforation, may be added in the later phases.

Sources of Infection.—That people do not "catch" enteric fever but either "eat or drink" it is an old medical saying which conveys the essential truth that the disease is brought about by ingestion (*vide* Chapter XXVII). Water contaminated with sewage; articles of food, *e.g.*, shellfish and watercress, grown in and gathered from contaminated water; dairy or cooking utensils washed in such water have proved to be the sources of infection in many an extensive outbreak in the past. Nowadays a sewage-contaminated water supply is, fortunately, a rarity in this country. Occasionally a defective sewer leaking into the water supply is discovered during or after the event of an epidemic; in rural and some semi-urban districts, water may still be obtained from shallow wells in the gravel or wells in the chalk connected, especially after a dry summer, by fissures with a cesspool at a higher level. Generally speaking, the water supply is above suspicion and is so maintained by systematic bacteriological tests (for coliform

organisms). Stringent regulations secure that oyster-beds are not laid in the vicinity of a sewer-outfall; mussels, however, nobody's property, cannot be brought under the same control and are, therefore, unless properly boiled, potentially dangerous. Watercress beds are carefully supervised and this plant has virtually ceased to be a source of danger.

General Incidence.—The effect of the measures taken by sanitary authorities has been manifest in the remarkable decline in the *death rates* of the enteric group of fevers in this country.

It has been observed (*Lancet*, 1937, ii., 1340) that "in 1871-75 the standardised death rate was 371 per million living, or seventy-four times as high as the corresponding figure of 5 per million recorded in 1931-35. . . . This fall took place in two stages; between 1871-75 and 1886-90 (15 years) the death rate was halved; there was a pause between 1886-90 and 1896-1900, and then a second rapid phase of improvement set in. . . . The first phase may be attributed to improvement in water supplies and drainage, and this was followed by a period of (administrative) stagnation; then came recognition of the problem of the carrier and a renewed downward course assisted, no doubt, by an increasing and stricter attention to the water supplies in still backward areas."

It may be added, as of possible significance, that in 1896 the paratyphoid bacillus was isolated by Achard and Bensaude, and that in the same year Almroth Wright introduced preventive inoculation with vaccines, and Grüber described specific agglutination, that property of the patient's blood serum upon which the Widal test (*q.v.*) is based. During the 'fifties and 'sixties of the nineteenth century enteric was *the* endemic fever of this country (Murchison). In the first decade of the present century the annual notifications might attain five figures; during the second decade there was a great decline, but during the third decade and in the last few years an increase in incidence is to be noted, although the numbers of cases notified vary considerably in individual years. Thus in each of the years 1927 and 1928 the notifications exceeded 3,500; in 1934 they were only 1,200; in 1936, some 2,500. A single local epidemic may account very largely for the increase in notified cases in any particular year. It would be quite wrong to suppose that recent outbreaks, or any notable proportion of them, are to be attributed to any slackening of precautions. Most of them have been traced not to any gross or continuing defect in the water supply but to carriers.

Thus an extensive outbreak in Bournemouth and neighbourhood in 1936, during which over 500 cases were notified, was due

to the consumption of raw milk sold by one dealer, the source of infection of the milk being ascribed to a carrier at the farm. An outbreak of paratyphoid-B in Liverpool and Bootle at the end of 1936 and the beginning of 1937 was ultimately traced to a carrier in a bakery "from which was derived the bread consumed by 62 per cent. of the patients, who numbered 123 (*Brit. Med. Jour.*, 1937, ii., 369). The crusts of loaves were infected as the result of handling.

Geographical Incidence.—The disease occurs, or is likely to occur, wherever the water supply is impure; generally speaking, the less satisfactory the sanitation the more prevalent is enteric fever. In India, an endemic area, as in the East generally, the disease, whether typhoid or paratyphoid, tends to be severe and to occasion high mortality.

Seasonal Incidence.—Typhoid fever in temperate climates is typically a disease of the autumn months. In this country, although there is a general low level of incidence throughout the year, most cases occur in September, October and November; there is then a fall. Paratyphoid fever exhibits the autumnal rise less markedly; it may provide numerous cases in the summer months. This is in part due to the fact that many outbreaks of paratyphoid originate in the contamination of food by carriers.

Age and Sex Incidence.—Older children and young adults are most frequently affected, but attack may occur from infancy to old age. Owing to the fact that in infants and young children, the disease, particularly paratyphoid, not infrequently takes the clinical form of acute gastro-enteritis (*vide* Chapter XXVIII), the real nature of the attack is not recognised. Thus the incidence of enteric fever in children under ten years of age tends to be underestimated. The age-incidence (and sex-incidence) is affected also by the source of infection; in milk-borne epidemics, women and children suffer proportionately in greater numbers. In the Bournemouth outbreak the age and sex incidence of cases was as follows: males, 115; females, 169; total, 284 at all ages. Children up to ten years of age provided 31·2 per cent. of the cases (45 boys and 43 girls: practically equal numbers). From that age onwards female cases predominated; 70 males to 126 females.

Case Fatality.—In different epidemics and in different countries the fatality rate of typhoid fever may range from 10 to 20 per cent.; that from paratyphoid fever between 1 and 2 per cent., but it is to be noted that some outbreaks of paratyphoid occasion a fatality rate approximating to that of typhoid. In the recent outbreaks already referred to, the

fatality rate of typhoid (Bournemouth) was 10·9 per cent., and of paratyphoid-B (Liverpool), 9 per cent. The maximum fatality rate of either typhoid or paratyphoid falls upon children under three years of age and upon adults aged upwards of sixty years. In these age groups it may reach 50 per cent. The minimum fatality rate occurs among children aged from five to ten years of age. (D. Harvey.)

Bacteriology.—*Bact. typhi* and *Bact. paratyphi* (*A* and *B*) are motile, gram-negative, non-lactose fermenters (*vide* Chapter XXVII). They are flagellate organisms and this fact has assumed great importance. The antigenic structure of all organisms of the salmonella sub-group is complex, different antigens being located in different parts of the organisms :—

(*a*) FLAGELLAR (OR H) antigens are present in the flagellæ ; they may be :—

- (i) in the *type-specific* phase, *i.e.*, the antigens assume a form which is specific for each organism ;
- (ii) in the *group* phase, *i.e.*, the antigens assume a common form in all members of the salmonella sub-group (except in *Bact. typhi* in which the group phase does not occur).

(*b*) SOMATIC (OR O) antigens are present in the body ; they are not so specific as the type-specific H, for *Bact. typhi* and *Bact. Gaertner* have one common antigen, and *Bact. paratyphi-B* and *Bact. typhi-murium* have another.

(*c*) In *Bact. typhi* an additional *virulence* (or *Vi*) antigen is known but is not yet related to any particular part of the organism.

Different cultures of the same organism vary in the quantity of H and O (and Vi) antigens present, so that H, O or Vi strains are obtainable.

A single culture may contain some colonies with H antigens in the group phase and others in the specific phase.

Each of these antigens stimulates the production of a corresponding agglutinin (H-specific, H-group, O and Vi). This fact has assumed great importance in recent years and the practical result has been a modification by Weil and Felix of the ordinary *Widal test.* The latter consisted of an examination of the serum for agglutinins without reference to H or O and anomalous results were sometimes obtained. To-day serum is examined for O and both types of H agglutinins, using appropriate suspensions of the organisms.

Pathology.—1. PATHOGENESIS.—The clinical phenomena which make up the symptom-complex of enteric fever are broadly divisible into three groups: (*a*) Early bacteræmia, giving rise to indefinite symptoms of illness during the stage of invasion; (*b*) localisation of the organisms in the Peyer's patches and lymphoid follicles of the small intestine, resulting in inflammation, ulceration and sloughing, and manifested clinically by enteritis; and (*c*) localisation in other organs and tissues, resulting in complications which may become evident clinically only when the intestinal disease is at an end.

The train of events after infection is as follows:—

The ingested organisms reach the intestinal tract. Many are destroyed but some are borne to the Peyer's patches and lymphoid follicles and ultimately, by passage through the walls of the gut, reach the mesenteric glands, which become inflamed, and the spleen, which becomes enlarged. In these tissues multiplication takes place; the defences break down and from the lymphatic glands the bacilli pass to the blood stream through the thoracic duct, and in a high proportion of cases may be cultured from the blood during the first weeks of the illness. Thence they pass to the viscera; the gall-bladder, in particular, is invaded early, the kidney and possibly bones and joints later on. With the gall-bladder as a focus or reservoir, reinvasion of the lymphoid structures of the small intestine takes place. This second invasion gives rise to an exacerbation of intestinal symptoms which has been held by some to be in the nature of an allergic phenomenon.

2. POST-MORTEM APPEARANCES.—Since death from enteric fever may occur early or late in the attack from lesions which vary with the stage of the disease, the post-mortem appearances are also variable. In children, and especially infants, the clinical picture may be quite unlike that seen in adults, and the pathological changes are correspondingly diverse.

(*a*) *Abdominal Viscera.*—*Intestines.*—The typical local lesions of enteric fever occur in the Peyer's patches and solitary follicles of the small intestine. In the early stages these structures are inflamed; later, ulcers are produced from which, finally, necrotic sloughs separate. The ulcers, which are countless, are characteristically *elliptical*; the *major axis* of the ellipse lies *along* not *across* the gut. The *edges* of the ulcers are crenated and shelving, not clear-cut. If the sloughs have separated, the *bases* of the ulcers will be seen to be smooth. In the process of separation of one or more sloughs, (*a*) a vessel in the wall of the gut may be eroded, in which case there will be evidence of blood in the bowel, but not

necessarily of its origin; or (*b*) the intestinal wall may be perforated. The perforation (there may be more than one) is usually small. Evidence of local or general peritonitis may be forthcoming. It is to be noted that in *paratyphoid* the lymph follicles of the large intestine, especially near the ileocæcal valve, may show similar changes. In young children the typical lesions may not be found, the appearances being those of acute or subacute enteritis. The *spleen* is enlarged, congested and very soft. The *liver* is usually somewhat enlarged and shows fatty degenerative changes and sometimes focal necrosis. There may be evidence of cholecystitis. The *kidneys* present changes similar in type to those found in the liver: small abscesses may be present.

(*b*) *Respiratory System.*—The naked-eye appearances of the lungs are rarely normal. If death has occurred early, *bronchitis* is usually evident; in adults, *broncho-pneumonia* is a later and less common finding, but in children it may be an early and predominant condition. *Lobar pneumonia* is less commonly found. With or without pneumonic changes, *hypostatic congestion* is frequently present in adults dying late in the attack.

(*c*) *Circulatory System.*—There is usually evidence of *myocarditis* which may be extreme in degree. The muscle is pale and flabby with areas of fatty degeneration. It may be so thin that the heart after removal "mushrooms" over the hand. One of the late complications is *phlebitis* with *thrombosis*; the left femoral vein is the commonest site. The limb may be œdematous. Death may result from *pulmonary embolism.*

(*d*) *Central Nervous System.*—There are usually no naked eye changes in the central nervous system. In infants and young children, *suppurative meningitis*, due to the specific organism, and possibly originating in the middle ear, may be the cause of death.

(*e*) *Skeletal System.*—The typhoid bacillus tends to invade long bones, giving rise to a quiet *osteomyelitis*. Paratyphoid bacilli produce similar lesions and may also invade joints, causing *suppurative arthritis*. Patches showing *Zenker's degeneration* may be found in the abdominal and other large muscles, such as the pectorals.

Blood Picture.—The blood picture in an enteric group infection may be of diagnostic importance. After the first two or three days of illness there is *neutropenia* with relative lymphocytosis, but marked *eosinopenia*. Eosinophils may be absent. The occurrence of complications of suppurative type is reflected in *polymorphocytosis*.

In the uncomplicated case the neutrophils begin to

increase towards the end of the third week. A post-infective *lymphocytosis* may occur.

The enteric fevers include typhoid and the paratyphoids, between which, on clinical grounds, differentiation cannot amount to more than surmise, while any clinical distinction between the paratyphoid fevers themselves is impossible. Nevertheless, as a group the paratyphoid fevers *do* exhibit features which are sufficiently constant to make separate consideration desirable. In children, enteric group infections may differ clinically so greatly from the disease in adults as to call for special mention. Thus the clinical description of enteric fever is divided into three sections: (I) Typhoid Fever; (II) Paratyphoid Fevers; and (III) Enteric Fever in Children.

I. TYPHOID FEVER

Incubation Period.—The incubation period ranges, as a rule, from twelve to fourteen days. Periods as *short* as eight to ten days or as *long* as twenty-one days occur.

Clinical Features.—The clinical description of a typical attack of typhoid fever may be divided into :—

STAGE I.—*Invasion.*—The characteristic mode of invasion is insidious; vague symptoms of illness tending to increase in severity throughout the first week. Lassitude, frontal headache, general aches and pains, disturbed sleep, anorexia and thirst, abdominal discomfort, with occasionally definite pain referred to the right iliac fossa, nausea or actual vomiting, constipation *or* diarrhœa are among the early symptoms To these may be added sore throat and a troublesome cough. Some degree of *bronchitis* is not uncommon. *Epistaxis* is not unusual. The patient's eyes are bright and his cheeks flushed. The tongue is thickly coated with white fur and is not notably dry. The mental state may be quite clear; irritability and a certain jerkiness of muscular movements may be noted.

Unfortunately for his subsequent progress the initial symptoms may be so slight that the patient continues his occupation until compelled by increasing prostration or some more definite catastrophe to go to bed. Such *ambulant* patients tend to do badly in the later stages of the attack.

Temperature.—If, as a suspect or otherwise, the patient comes under observation early and a morning and evening record of his temperature is obtained, the typical step-ladder rise may be noted. From some initial level, such as 101° or 102° F. in the morning, the temperature rises by a degree—more or less—in the evening and falls again the following

morning, but not to the level recorded on the preceding day. Thus during the first week the indefinite symptoms of illness are accompanied by progressively increasing pyrexia; the evening temperature by the end of the first week may reach 104° F. During the stage of invasion the pulse rate is usually increased, but not always proportionately to the temperature. The pulse is full, but somewhat soft.

STAGE II.—*Advance.*—The first stage of the illness merges into the second, and the clinical picture alters. There is a change for the worse in the physical and mental condition; the characters of the temperature chart and of the pulse are modified, and there are definite signs of the real nature of the disease from which the patient is suffering.

General State.—Lassitude and headache give place to prostration and hebetude, with muttering delirium particularly at night. The eyes are heavy, possibly sunken, and the facial muscles lack tone; the cheeks are flushed, but the expression is one of intense weariness. The tongue is dry and covered with a brown fur; on protrusion fine tremors may be noted. The mouth tends to become foul; sordes collect around the lips. (Herpes labialis is rare in typhoid, less rare in the para-typhoids.) Usually there is obvious loss of flesh. There may be abdominal distension, but this is by no means invariable; it is unusual if the patient has come under treatment early.

The temperature remains high with but slight morning remissions. The pulse tends to become slower and softer than during the first week. Absolute bradycardia, although common in convalescence, is not usual in the earlier stages; the pulse is soft but of good volume. From about the end of the first week until the middle of the second week a dicrotic wave may be detected, but this is by no means constant. From the beginning of the second week of the illness two important physical signs are to be noted, viz., *enlargement of the spleen* and an eruption of *spots.*

The *spleen* may at first be enlarged to percussion only, but later may be palpated one to two fingers' breadth below the costal margin. The edge, which in the early stage is quite definite, may become soft and indefinite. Palpation must be carried out gently; not only is the spleen tender on pressure but it may be damaged by vigorous examination. As a complication, rupture of the spleen is of very rare occurrence.

The typical *eruption* consists of lenticular rose-coloured spots which appear in crops and may continue to appear from the beginning of the second week until the illness is far

advanced. The spots are the cutaneous manifestations of bacteræmia and contain the causal organism.

The usual *sites* at which the spots should be sought, and when found ringed with a skin pencil, are the sides and back of the chest, particularly between the shoulders, and the upper abdomen. Occasionally the eruption occurs in other situations, *e.g.*, the face or the arms. In typhoid (*cf.* paratyphoid) the number of spots in a single crop is usually sparse; there may be only one or two. They are slightly raised and disappear momentarily on pressure, and in about two days fade away to be succeeded or not (there may be only a single crop) by more in other situations. The eruption of rose spots is by no means constant. The spots must be distinguished from the lesions of folliculitis, sudaminal eruptions, tiny nævi, petechiæ and insect bites.

Stools.—During the first week the patient may have diarrhœa or may be constipated, and in some cases tends to be constipated throughout the attack. Usually, however, during the second week the passage of a typical "pea-soup" stool is first noted (*vide* Table XXII, Chapter XXVII). Pea-soup stools may continue to be passed for a variable number of days; at first they tend to be frequent (exceptionally 20 or more per diem may be passed), but as the intestinal lesions heal, *i.e.*, after the end of the third week of illness, the stools are passed less frequently. During the third week *sloughs* derived from the Peyer's patches may be present in the stools and should be sought. Every stool passed should be reserved for examination, special attention being paid to the occurrence of *blood*. Anything more than streaks of blood must at once be reported by the nurse: *melæna*, of course, is of serious import.

Gradually the stools become not only less numerous but semi-formed, and at length normal in consistency.

In some cases (particularly in paratyphoid) pea-soup stools are never passed; they may be semi-formed or of normal consistency throughout, and as already mentioned, constipation may be a troublesome feature of the illness.

Urine.—*Albuminuria* is common at the onset and may persist. The amount of urine passed is usually diminished: the specific gravity is high and the reaction ordinarily acid. *Indicanuria* is characteristic. *Bacilluria* during the second week and later may occur: the causal organism may be isolated in almost pure culture.

Progress.—The fastigium is of variable duration, but may continue from ten to fourteen days or longer. During the

whole of this period the patient is in danger either from the effect of toxæmia upon the myocardium or from an intestinal calamity. To these may be added the perils of the "typhoid state" (see Chapter V, p. 38). If he survives this critical period, the general condition commences slowly to improve. The toxæmia abates; the intestinal lesions heal. There is a gradual fall of temperature; *lysis* is the rule, *crisis* the exception. The last week or so of pyrexia may be almost a mirror-curve of the first, showing a step-ladder fall instead of a rise. The mental state becomes progressively clearer; the tongue cleaner. The stools become less numerous and lose their pea-soup character; instead, they are at first semi-formed and later may be constipated. Urine is again passed which is normal in quantity and quality. With improved appetite and digestion the patient loses his haggard and emaciated appearance and commences to gain weight. The myocardium partly regains its tone, but complete restoration, as in diphtheria, may not occur for some time.

During the stage of *decline* no nursing precautions must be relaxed, nor must the physician give other than a guarded prognosis, since *recrudescence* is by no means uncommon. The temperature rises again; toxæmia recurs, possibly fresh crops of rose-spots appear, and pea-soup stools are passed once more or, if they have not yet ceased, passed with increased frequency. The patient is again in danger. A recrudescence is usually not of long duration, but it may add considerably to the length of the illness.

The temperature at length returns to normal, and the patient becomes convalescent.

STAGE IV.—*Convalescence.*—The main point in considering convalescence as a separate stage of the disease is to emphasise the importance of its proper management. The patient is still a sick man: his nutrition is poor, his myocardium flabby; he may yet develop phlebitis and thrombosis, or more serious, a *relapse,* in which case the illness starts *de novo*. Generally, a relapse is of shorter duration and lesser severity than the original attack, but it may be more severe, and hæmorrhage or perforation prove fatal. Second and third relapses sometimes occur. Rise of temperature during the decline or convalescence is not necessarily due to relapse of the general disease: it may be due to some intrinsic or extraneous complication.

Second attacks of typhoid fever occurring months or years after the first are rare, but an attack of typhoid in no way protects the patient against *paratyphoid.*

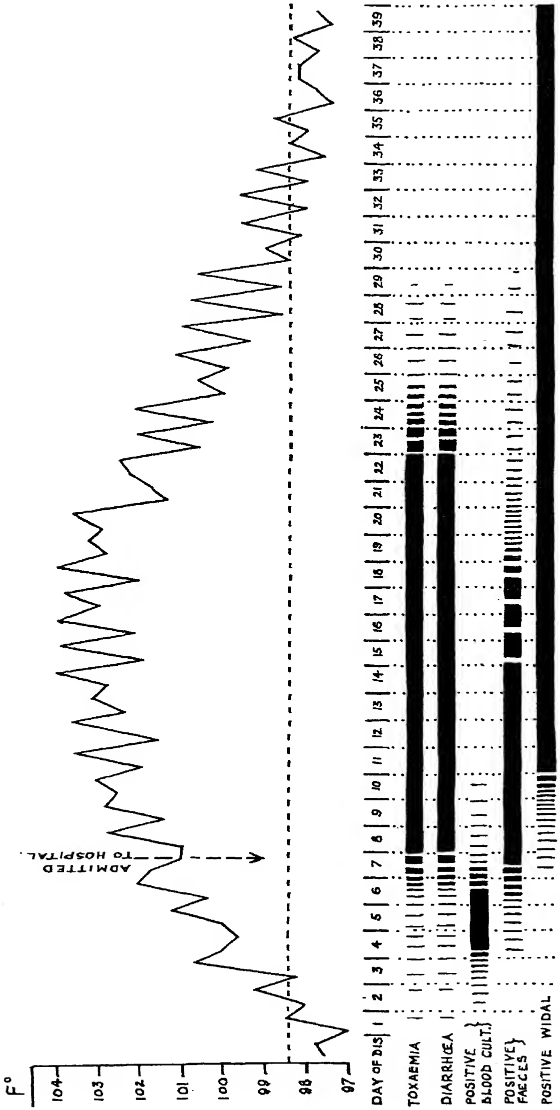


FIG. 31.—Typhoid Fever; example of a typical attack of considerable severity, but without complications.

II. PARATYPHOID FEVER

As already stated, it is virtually impossible on clinical grounds to differentiate between typhoid and paratyphoid fever in any given attack, and quite impossible to decide clinically as between the paratyphoids themselves.

Nevertheless, paratyphoid infections as a group do exhibit general characteristics which may be summarised as follows :—

1. The incubation period is shorter.

2. The mode of onset tends to be more abrupt and is frequently atypical ; much more frequently than in typhoid the initial illness may resemble acute gastro-enteritis, "influenza," or the outstanding finding may be broncho-pneumonia.

3. The duration of the attack is frequently shorter : the temperature may return to normal in from ten to fourteen days ; but it must be noted that this is not constant, and that attacks of paratyphoid fever occur in all respects comparable in duration and severity to typhoid, even of the most severe form.

4. The typical temperature chart of paratyphoid shows wider remissions : even during the fastigium there may be a difference of a degree or a degree and a half between the morning and evening temperature.

5. The eruption in paratyphoid, particularly perhaps in paratyphoid-A, tends to be more profuse than in typhoid. It may appear so profusely upon the face as to be mistaken for measles. The deeper colour of the spots and their more markedly maculo-papular character increase the resemblance. On the other hand, the eruption may fail to appear. In a recent epidemic only 47 per cent. of the cases exhibited a rash.

6. The degree of toxæmia is usually less and intestinal complications are infrequent. Nevertheless, the degree of toxæmia and the likelihood of hæmorrhage or perforation must never be underrated, and precautions in all respects as great as those taken in the case of typhoid must be enjoined. The premature return to normal life of a patient who has suffered from an unsuspected or a supposedly mild attack of paratyphoid fever may have as a sequence sudden collapse and death from myocardial failure.

Paratyphoid-C (Hirschfeld). Illnesses clinically indistinguishable from the other paratyphoid infections have been recorded in which the causal organism was a strain of paratyphoid very closely resembling in its cultural reactions *B. suipestifer*, but serologically distinct from *Bact. paratyphi A* and *B*.

III. ENTERIC FEVER IN CHILDREN

The younger the child the less does the clinical picture of typhoid or paratyphoid conform with that seen in adults. It is as a rule only in children upwards of five years of age that there occurs an approximation to the adult type of illness.

In infants and very young children the onset tends to be abrupt and characterised by a convulsion and sharp rise of temperature. The commonest form that enteric fever assumes in infants is acute gastro-enteritis: this is particularly true of paratyphoid (*vide* Chapter XXVIII). The illness may be characterised mainly by *broncho-pneumonia*, gastro-intestinal symptoms being absent or but little marked.

Signs of meningitis may dominate the clinical picture. These may prove to be meningism at the onset of the gastro-intestinal type or may be true meningitis, the causal organism, more commonly *Bact. paratyphi-B.*, being present in the cerebrospinal fluid. Occasionally in infants meningitis is a terminal event.

Finally, the infection may produce no identifiable localised lesions, the infant dying of general septicæmia (see Infectious Enteritis of Children and Dysentery, Chapters XXVIII and XXIX).

In a recent epidemic (V. Shaw, 1937) the onset in younger patients was sharp with headache, nausea and pyrexia (104° to 105° F.), and abdominal discomfort; or the attack commenced with cerebral irritation, stupor, squint and the meningeal cry. Broncho-pneumonia was an early feature of other cases, and in others again the genito-urinary system was mainly involved. In an epidemic of paratyphoid-B, reported by W. M. Frazer *et al* (1937), it was noted that the onset was abrupt with abdominal symptoms simulating an "acute abdomen." Occasionally true appendicitis, due to the causal organism, occurs at onset.

On the other hand an institutional outbreak of paratyphoid is on record in which the earlier cases resembled, and were regarded as, influenza until children suffering from a more typical attack revealed the true nature of the infection.

In children, the eruption tends to be sparse; it frequently fails to appear at all. Transient rashes of scarlatiniform type may, however, occur in the early stages. Greater remissions of temperature during the fastigium are usual in both typhoid and paratyphoid. Dicrotism is only to be noted in severe attacks in older children. Recrudescence or relapse is of more common occurrence than in adults. Complications are less frequent, hæmorrhage and perforation being rarely encountered.

Complications of Enteric Fever.—The complications of typhoid and paratyphoid are identical in character, but in general occur more frequently in the former than in the latter, with the possible exception of suppurative arthritis. They are conveniently grouped as follows :—

I. GASTRO-INTESTINAL TRACT.—(*a*) *Meteorism.*—Some degree of abdominal distension due to the accumulation of flatus in the atonic intestine is not uncommon during the fastigium, but, if considerable, may by pressure through the diaphragm embarrass the already feeble heart muscle and cause syncope. Further, the stretching of the intestinal wall at the critical period of the separation of the sloughs enhances the danger of perforation.

(*b*) *Hæmorrhage.*—Intestinal hæmorrhage, slight or severe, is estimated to occur in 7 per cent. of cases of typhoid : it is less common in paratyphoid. The most usual time is towards the end of the third week when the sloughs are separating. The amount varies from mere streaks of blood mixed with fæces to the passage of a stool which consists mainly of blood. Streaks of bright blood passed with a constipated stool may, however, be of rectal origin. Depending upon the site of hæmorrhage and the length of time which elapses between its occurrence and the passage of the stool, the blood in true intestinal hæmorrhage may be bright, or relatively so, or tarry, *i.e.*, melæna. In the latter event the patient may be at the point of death before the cause becomes obvious from the appearance of the stool.

Hæmorrhage is to be suspected in a patient who suddenly becomes apprehensive and complains of vague abdominal discomfort and a "sinking feeling." The face becomes pale and sometimes covered with sweat, the pulse increasingly rapid and thready. There is a sudden or rapid fall in temperature to subnormal. Unless prompt steps are taken to control the bleeding and replace the lost fluid, fatal syncope is the result.

(*c*) *Perforation.*—Perforation occurs in some 3 per cent. of cases of typhoid, the cause being the same as in hæmorrhage, *i.e.*, the separation of the sloughs. It is most likely to take place at the same stage of the disease : indeed, both hæmorrhage and perforation may occur simultaneously. Since the treatment of either condition is urgent, but quite different, it is of the utmost importance to distinguish between perforation and an occult hæmorrhage.

Whereas the evidence of hæmorrhage prior to the passage of a stool tends to be ill-marked, the occurrence of perforation

gives rise as a rule to sudden abdominal pain, continuous or spasmodic, referred by the patient to the right hypogastrium or right iliac region. The mental and physical state caused by a considerable hæmorrhage is intensified in perforation: this is in part due to the abdominal pain and in part to shock and collapse. But the intensity of pain and its duration are variable. In the emaciated feeble patient, pain may be slight and transient, and if overlooked, be fatally misleading. Any degree of abdominal pain should lead to careful palpation in order to elicit which of the abdominal muscles are "on guard." This localised muscular rigidity, intensified on palpation, which also elicits tenderness, is sufficient evidence to justify an exploratory laparotomy.

It has been held that the disappearance of liver dullness is a sign of perforation, but it is inconstant and late, and of little value if meteorism exists. Vomiting in the early stages sometimes occurs but is not constant. The temperature is variable. There may be a sudden drop due to shock and collapse, or a rise followed by a fall, and then a further rise some hours later with the onset of *general peritonitis*. Unless diagnosis, laparotomy, and suture of the perforation (or perforations) are speedy, this complication is the almost inevitable sequel.

It is true that some patients have recovered from a typhoid perforation without operation, the lesion having become shut off by lymph or adhesions, but even with prompt surgical measures the outlook is very poor.

A few cases of typhoid-peritonitis without perforation are on record. It is unnecessary to describe the clinical picture of general peritonitis; the repeated vomiting, pyrexia, general abdominal pain and rigidity and the terminal Hippocratic facies are unmistakable.

(*d*) *Cholecystitis.*—Acute cholecystitis, sometimes transient, but which may become suppurative, is an occasional complication in either children or adults, and may require prompt surgical measures. Mild grades of cholecystitis may pass unnoted and result, especially in middle-aged women, in the formation of gall-stones. The patient may become a *biliary carrier* (*q.v.*).

(*e*) *Appendicitis.*—The attack of enteric fever may commence with appendicitis, or this complication may occur at any stage. The frequency of the "abdominal-emergency" mode of onset in children has already been mentioned. If symptoms suggestive of appendicitis occur later in the attack, the greatest care must be taken to differentiate appendicitis from perforation, and it may be that even in what appears

to be a mild attack of appendicitis, which ordinarily would be treated on expectant medical lines, an exploratory laparotomy is advisable.

(*f*) *Parotitis*.—Parotitis in the acute stage of the disease may be, rarely, of hæmatogenous origin, but is more likely to be due to an extension of oral sepsis, the result of neglect of the hygiene of the mouth. Suppuration of the gland is usual, and prompt surgical measures are necessary in order to limit the process which may otherwise involve neighbouring structures. Suppurative parotitis is a serious complication, not only for this reason, but because the accompanying trismus may make it necessary to feed the patient through a straw and, of course, enhances the difficulty of keeping the mouth clean. There is therefore a liability to aspiration-broncho-pneumonia and death from septic absorption. Mild non-suppurative parotitis may occur during the convalescent stage. *Splenic abscess*, *rupture of the spleen*, *pancreatitis* and *jaundice* are rare events in enteric fever.

II. GENITO-URINARY.—*Albuminuria* of toxic origin is the rule rather than the exception in a case of any severity. But in some cases of enteric fever the genito-urinary system bears the brunt of the attack, the illness commencing with acute nephritis.

Pyelonephritis and *pyonephrosis* are occasional complications.

One or more small abscesses in the kidney are the usual reservoirs of infection in urinary carriers. Bacilluria is so common as hardly to be regarded as a complication. It may be associated with cystitis due either to enteric or coliform organisms.

Retention of urine must be apprehended, particularly during the typhoid state (*q.v.* Chapter V); *suppression* is rare. *Orchitis*, usually unilateral, sometimes suppurative and resulting in permanent damage, is an occasional late complication.

III. RESPIRATORY SYSTEM.—Enteric fever may commence with signs and symptoms chiefly referable to the respiratory tract. Thus the illness may sometimes simulate influenza, with or without localising signs, or it may commence with laryngitis, bronchitis, broncho-pneumonia, lobar pneumonia or pleurisy. Laryngitis is usually transient, but may result in ulcerative lesions of the larynx and stenosis.

The onset with broncho-pneumonia is not uncommon in paratyphoid in children, and some degree of bronchitis is usual in adults in early stages of enteric. Broncho-pneumonia, and,

much less frequently lobar pneumonia, may occur as a complication at any stage.

In the elderly patient, especially, hypostatic congestion is not uncommon in the later stages: it may be followed by broncho-pneumonia, which is then usually fatal.

IV. CIRCULATORY SYSTEM.—(*a*) *Myocarditis*.—The outstanding cardiac lesion is myocarditis which may become extensive in degree and be the actual cause of death, but some degree of myocardial degeneration is almost inevitable and its existence should be presumed even if not clinically evident. It follows, therefore, that convalescence must be prolonged and most carefully managed, lest sudden cardiac failure result from undue exertion.

The signs of myocardial involvement in typhoid are identical with those of toxic myocarditis of any causation.

(*b*) *Endo- and Pericarditis*.—Having regard to the fact that the causal organisms invariably invade the blood stream, it is remarkable that endocarditis or pericarditis are such uncommon complications.

(*c*) *Arteritis*, and especially *phlebitis*, are usually late complications, affecting most commonly the large vessels of the lower limbs. The *right* femoral, popliteal or tibial arteries are the most frequent sites of arteritis: the *left* femoral or saphenous veins of *phlebitis*. Arteritis may result in *gangrene* of the part supplied: phlebitis in *thrombosis* with œdema of the limb. Phlebitis, as a rule, occurs only in patients over ten years of age. Embolus is rare, but in a recent epidemic a child died suddenly from pulmonary embolism.

V. NERVOUS SYSTEM.—(*a*) *Mental States*.—*Delirium* of muttering type may occur during the invasion period, but is more usual at the height of the disease. It is occasionally violent and the patient may need restraint. The mental condition in the typhoid state is usually stuporose, passing in the fatal case into terminal coma vigil (*vide* Chapter V).

Psychoneuroses, probably exhaustion states, may occur during convalescence after a severe attack, but true *psychoses*, such as mania and melancholia, may develop and become permanent. *Korsakoff's syndrome* (*psychosis polyneuritica*) has occurred in connection with typhoid, and is particularly liable to do so in the alcoholic subject.

(*b*) *The meninges* may be affected thus: (i) Meningism at the onset; (ii) typhoid—or paratyphoid—meningitis, either at the onset (particularly paratyphoid in children), during the height of the attack or as a terminal event; (iii) secondary pyococcal meningitis, possibly otogenic, may occur at any stage.

(*c*) *Encephalitis* with the Parkinsonian syndrome has been reported (*vide* Chapter XXVI, p. 328).

(*d*) *Hemiplegia* due to thromboses and sometimes associated (particularly in children) with *aphasia* is uncommon.

(*e*) Various *paralyses*, such as Landry's ascending type, are of rare occurrence.

(*f*) *Peripheral neuritis*, which J. D. Rolleston believes to a considerable extent to be due to the excessive therapeutic use of alcohol, is usually generalised. Neuritis of individual nerves, such as the external popliteal, has been recorded. The condition known as "tender toes," in which the toes become, temporarily, hyperæsthetic, so that the patient cannot endure the bed-clothes to touch them, Osler believed to be "probably a local neuritis in some, but in others due to phlebitis."

VI. SPECIAL SENSES.—1. *Ears*.—Temporary deafness is not uncommon. Otitis media results from an extravenous infection of the upper respiratory tract, not from the causal organism, and its occasional occurrence is fortuitous.

2. *Eyes*.—Due to the condition of general asthenia, extraneous infective conditions of the conjunctiva and globe, such as conjunctivitis, keratitis and iritis may occur. Optic neuritis and strabismus are rare.

VII. BONES, JOINTS AND MUSCLES.—*Arthritis*, usually suppurative, tends to be more common in paratyphoid than typhoid. *Bact. paratyphi-B.* was first isolated by Achard and Bensaude from a suppurative lesion of a joint. Characteristic of enteric group infections are silent *bone abscesses* which may not become clinically evident for years after the attack. Pure cultures of the organism may be obtained and hence the pus is a potential source of infection.

"Typhoid spine," or *spondylitis*, is another characteristic lesion, which makes its appearance in early convalescence and, as a rule, is confined to adults. The condition results from the absorption of intervertebral discs, and commences with sudden pain in the lumbar region. Suppuration is rare. Many weeks may be required for repair and restoration of function, usually secured at length by rest and immobilisation, the patient being nursed in a supine posture.

Muscles.—Patches of Zenker's degeneration of the large muscles, such as the rectus abdominis and pectoralis major, may result in painless rupture. If the patient survives the illness, complete repair ultimately occurs.

Skin.—Staphylococcal infections of the skin, furunculosis and small subcutaneous abscesses are prone to occur during convalescence.

Bed-sores, due to local pressure-necrosis, may result in the death of the patient from septic absorption. The formation of bed-sores is constantly to be apprehended and, with rare exceptions, is to be avoided by skilled nursing.

ASSOCIATED INFECTIONS.—It is obvious that the infections most likely to be associated with enteric fever are those which are also water-borne, *e.g.*, the dysenteries and cholera, the causal organisms of which have been ingested at the same time. Various combinations occur in the tropics, the enteric group infection owing to the longer incubation period making its appearance during what would ordinarily be the convalescent stage of the first disease.

Various *extraneous* specific infections, *e.g.*, diphtheria, are met with from time to time. An attack of malaria may add not only to the gravity of the patient's condition, but to the difficulty of diagnosis.

Sequelæ.—The mental condition has already been mentioned. The psychoneuroses, the exhaustion states, at length clear up with specialised treatment: the psychoses may become permanent. *Chronic cholecystitis,* with or without gall-stones, is of clinical and public health import. The same may be said to a lesser degree of the silent *bones abscesses* already mentioned. *Alopecia* is an occasional sequel: it is more likely to occur in children. The hair ultimately grows again.

Aids to Diagnosis.—It is wise, unless there is definite evidence to the contrary, always to bear in mind the possibility that a febrile illness, be the onset insidious or sudden, may be an enteric group infection. It is true that absolutely afebrile attacks are on record, especially in children, but such are excessively rare: there is at least *some* degree of fever which may only be recorded if the temperature is taken at four-hourly intervals. Clinical diagnosis does not suffice; confirmatory measures are essential.

Blood Count.—Differential blood counts may be of the utmost assistance. Within the first three or four days the blood count in a case of suspected enteric may show the typical leucopenia with relative lymphocytosis, but with a notable reduction, possibly a complete absence, of eosinophilis (*vide supra.*) (Note that in malaria there also occurs, if the blood is taken at the cold stage, leucopenia with relative lymphocytosis, although during the hot stage there may be absolute lymphocytosis.)

Blood Culture.—Provided that the technique of collection is properly carried out at the right stage of the illness, blood

culture is successful in a high proportion of cases. The optimum time is the fifth or sixth day of the illness. Blood culture attempted late in the disease is less likely to be positive *but should always be performed.* It is essential to ensure absolute sterility of syringe, needles and skin.

Mackie and McCartney (1938) advise either (1) a 10 c.c. record syringe, with firmly fitting needle, sterilised by *boiling*, not hot air; (2) an "all-glass" syringe sterilised in the hot-air oven; or (3) as most convenient for private practice, the Bayer venules which are already sterilised, and may be obtained with bile-medium ready prepared to receive the blood.

Mere painting of the skin with iodine is not sufficient to ensure that the culture is not contaminated by skin organisms. It should be treated with ether and then alcohol, and finally, if preferred, iodine also. The veins at the bend of the elbow are made turgid by means of a tourniquet, and by making the patient grasp a roll of bandage.

At least 5 c.c., and preferably 10 c.c., of blood are withdrawn, the tourniquet removed and the puncture sealed with collodion. Unless a prepared venule is used, the blood must be at once introduced into bile-salt medium, which is then immediately transmitted to the laboratory for incubation and for further investigation.

Stools and Urine.—Until recently, the isolation of the causal organism from the stools, and particularly from the urine, has been regarded as a procedure only likely to be successful from the commencement of the second week of the illness onwards, and therefore at a stage when clinical and serological investigations might have already established the diagnosis. Thus in the Liverpool outbreak of paratyphoid-B, referred to earlier, Frazer *et al.* (1937) record that fæcal cultures were positive in 83·3 per cent. of first-week patients, 94·2 per cent. of second-week patients, and 92 per cent. of third-week patients.

Glass and Wright (1937), to obtain these results, employed duplicate plating on a brilliant green eosin agar medium (Jones) with and without previous enrichment in tetrathionate broth. The examination of urine in the early stages does not possess the same value, although later the fæces in some cases may be negative and the urine positive: therefore specimens of both should be collected. Glass and Wright make it clear that their results were obtained in paratyphoid-B, and although they believe that they would be similar in the case of typhoid, they are doubtful about paratyphoid-A, which does not grow well in tetrathionate broth.

Caution.—It is emphasised that the greatest caution must be observed in the collection of specimens of fæces or urine in order to avoid contamination of the hands.

Agglutination Tests (*Widal test and its modifications*).—It has already been stated that as the result of an enteric group infection, the patient's serum may contain agglutinins of three types: (1) flagellar (H), (*a*) specific, (*b*) group, and (2) somatic (O). Agglutinins of one or more types are demonstrable, as a rule, from the beginning of the second week of the illness. The dilutions of the patient's serum which produce clumping are at first low. The titre increases during the illness, but subsequently declines to some residual level which may persist for years and probably is never entirely lost. To possess diagnostic significance during the attack the patient's serum should agglutinate the organisms in the following (or higher) dilutions :—

Bact. typhi, 1 in 60.
Bact. paratyphi-A, 1 in 30.
Bact. paratyphi-B, 1 in 120 (Mackie and McCartney).

These figures are arbitrary and the titres vary with the same serum if different suspensions of the organism are used for testing. Results from different laboratories are therefore seldom comparable. The Medical Research Council has introduced standardisation: suspensions used in laboratories are compared with a standard and a *reduction factor* obtained; results are multiplied by this factor and the resulting titres are comparable wherever the serum is tested. Of more importance is a *rising titre*. A single titre of $\frac{1}{30}$ may be of doubtful significance, but a rise from $\frac{1}{10}$ to $\frac{1}{30}$ in the second week is definitely positive. It is therefore of considerable importance to perform the test at the earliest possible stage, so as to be able to note any changes in titre.

It is important to remember that agglutinins are produced not only as the result of a natural attack of typhoid or paratyphoid, but following preventive inoculation with typhoid-paratyphoid vaccine (T.A.B.) (*vide infra*). Therefore it must always be ascertained whether the patient has had (*a*) a previous attack of enteric fever and/or whether (*b*) he has at any time been inoculated with T.A.B. vaccine. The results of agglutination tests must be interpreted in the light of this information.

Thus, although second attacks of typhoid are rare, and combined attacks of typhoid and paratyphoid uncommon,

typhoid followed at an interval of months or years by paratyphoid, or vice versa, is less uncommon. Agglutination reactions might thus show a low level of residual agglutinins in respect of the past attack of typhoid or paratyphoid, and agglutination in higher dilutions of the organism responsible for the present illness. A second test would reveal the same titre of residual agglutinins, but a still higher titre due to the current infection, and would thus possess great diagnostic value.

Results in the Inoculated.—Artificial immunisation with T.A.B. vaccine stimulates the production of H and O agglutinins for each of the organisms, H particularly appearing in high titre. Subsequently there is a decline in both, but whilst O may almost or quite disappear, some residual titre of H agglutinins is common but is rarely at the same level for all three organisms. *Thus a single agglutination test in an inoculated person suspected to be suffering from enteric fever possesses no value,* unless the titre at which one organism is agglutinated far outruns the others ; even then it is not pathognomonic.

An attack of enteric fever in an inoculated person will stimulate both H and O agglutinins, resulting in a *rising titre* ; but a rise in H agglutinins can occur not only in enteric fever but also in *any* febrile illness—the *anamnestic reaction.* So that, in an inoculated person even *a rising titre of H-agglutinins does not necessarily mean an attack of enteric fever* ; whereas a *significant titre of O-agglutinins* (except in those recently inoculated), or better, *a rising titre of O-agglutinins,* provide evidence of active disease. Thus O-agglutinins indicate activity and H specific agglutinins provide information as to the type of enteric fever present. For these reasons the Weil-Felix modification of the Widal test is now invariably performed and should be repeated, preferably more than once.

J. S. K. Boyd (1939), reviewing the significance of tests for *Vi-agglutinins* (applicable to *typhoid* fever only), points out that these agglutinins appear early and disappear early, and their presence is of considerable diagnostic value between the first and fifth days of the disease (Bhatnagar).

Undulant fever (*q.v.*) may simulate enteric fever, especially paratyphoid fever, so closely that it is now customary to seek information as to the presence of *brucella* agglutinins at the same time.

Collection of Blood for Widal and Weil-Felix Tests.—Although in exceptional circumstances the microscopic method of performing the Widal test is still performed, it has been superseded almost entirely by the *macroscopic* or *flocculation* method. Whereas

the old method necessitated only a small quantity of blood collected in a Wright's capsule from the tip of the finger or lobe of the ear, for the *macroscopic* method, especially if the Weil-Felix modification and the test for *abortus* agglutinins are desired, 10 c.c. of blood are required. This is collected from a vein, very conveniently in a Bayer venule, with the same precautions as are observed in obtaining blood for culture.

For the details of performance of the tests a textbook of practical bacteriology must be consulted.

Diazo-reaction.—Ehrlich's diazo-reaction is usually positive from the second week onwards, but may also be positive in *e.g.*, *B. coli* infections, measles and tuberculosis. Thus, a negative reaction—by excluding enteric fever—may possess greater diagnostic value than a positive result.

Equal volumes of a saturated solution of sulphanilic acid (freshly dissolved in 5 per cent. HCl) and urine are mixed in a test tube, and then a few drops of 0·5 per cent. sodium nitrite solution, also freshly made. The mixture is shaken until it is quite frothy. The test is *positive* if on the addition of a similarly small amount of ammonia a deep cherry-red colour is imparted to the mixture.

Differential Diagnosis.—The diseases which must be excluded fall into two main groups : *Group A*, in which the mode of onset and advance more or less closely resemble the usual clinical picture of the toxæmia of enteric fever, and *Group B*, which includes conditions characterised by an abrupt onset with pyrexia and the general clinical picture of an acute toxæmic state.

Group B may be subdivided into (*a*) conditions in which gastro-intestinal symptoms are prominent, and (*b*) conditions in which there are localising signs in the respiratory tract or the central nervous system ; (*c*) conditions in which no localising signs are manifest, at any rate at first.

It will be recalled that in children especially an enteric group infection (in particular paratyphoid) may present the clinical picture of (i) gastro-enteritis, (ii) broncho-pneumonia, and (iii) meningitis.

GROUP A.—Onset and advance suggestive of enteric fever.

1. Infections caused by *B. coli* may give rise to a clinical picture which simulates very closely the early stages of enteric fever, including the suggestive step-ladder rise of temperature during the first week, *e.g.*, *B. coli* bacillæmia and pyelitis.

2. *Brucella* infections (*vide* Chapter XXXI, Undulant Fever).
3. *Tularæmia*, a disease of rodents caused by the *B. tularense*, which is serologically allied to *Brucella abortus* and *melitensis*. Other than laboratory infections, the organism is more usually conveyed by insect bites, and not as the result of handling infected rodents, *e.g.*, rabbits. The primary lesion is an ulcer of the skin which may be overlooked. The main symptoms as recorded by Bernstein (1935) and Amoss and Sprunt (1936) were continued pyrexia and toxæmia, prostration and delirium, tachycardia, dyspnœa, cyanosis, constipation and abdominal distension. The condition may be confused with enteric fever or miliary tuberculosis. Agglutination may be positive for *B. tularense*, but the patient's serum in low dilution may also agglutinate *Brucella abortus*.
4. *Hœmolytic streptococcal* infections : bacteræmia, subacute sinusitis, progressive endocarditis (which may also be caused by *S. viridans* strains).
5. *Tuberculosis :* miliary tuberculosis or tuberculous meningitis.
6. *Infective mononucleosis* (*vide* Chapter XX, Glandular Fever). Especially in the febrile type, an eruption may occur which resembles that of paratyphoid fever.

GROUP B.—(*a*) *Onset with marked gastro-intestinal features.*

1. Salmonella infections, other than typhoid or paratyphoid, so-called "food-poisoning" due to, *e.g.*, *Bact. gaertner* or *Bact. typhi murium* (*vide* Chapter XXVII).
2. Bacillary dysentery (*vide* Dysentery, Chapter XXIX).
3. "Influenza" of gastro-intestinal type.
4. The "acute abdomen," viz., appendicitis, cholecystitis pancreatitis, pneumococcal peritonitis and (rarely) the abdominal type of glandular fever (*q.v.* Chapter XX).
5. Psittacosis (*q.v.* Chapter XXXII).
6. Epidemic jaundice (*q.v.* Chapter XXXIII).

GROUP B.—(*b*) *Lobar pneumonia* (note the rarity of herpes labialis in typhoid ; less rare, however, in paratyphoid), *broncho-pneumonia*, *cerebrospinal fever*, *mastoiditis*.

GROUP B.—(*c*) "Influenza," *toxic scarlet fever* (*q.v.* Chapter XII), *malaria* : in the "cold" stage there may be leucopenia, but without the characteristic eosinopenia of enteric fever ; during the hot stage there is usually lymphocytosis. So that apart from the finding of the parasite in the red cells or the

presence of characteristic stippling, the differential white count may afford assistance if carried out in both the apyrexial and pyrexial stages. It is to be borne in mind, however, that an infection such as enteric fever tends to precipitate an attack of malaria in the malarial subject, and that both conditions may coexist.

Typhus Fevers (*q.v.* Chapter XXXIV).

Prodromal (*toxæmic*) *stage of smallpox* (*q.v.* Chapter XXII).

It is clear that in order to arrive at a definite diagnosis of many, indeed most, of the diseases mentioned above the clinician must have the assistance of the hæmatologist and bacteriologist. Read in conjunction with the clinical findings the *blood count* alone may enable a broad distinction to be made early between an enteric group infection and diseases caused by other organisms, but it is important not to rely upon one count unless the blood picture is unequivocal.

Blood culture should *never* be omitted and includes, of course, the identification of any organism which may be present in the peripheral circulation.

Tests for *agglutinins* should be carried out not only for the Salmonella group but for the bacillary dysenteries and brucelloses. Bacteriological examination of *stools* and *urine* should include the identification of any or all non-lactose fermenting organisms which may be isolated. Examination of the *sputum* and *cerebrospinal fluid* occasionally provides the clue ; *Bact. paratyphi-B* has been recovered in both broncho-pneumonic and meningeal types of the disease.

Treatment.—A. GENERAL MEASURES.—1. *Nursing.*—Skilled nursing is the most important factor, and the general measures for securing absolute rest should be rigidly observed (*vide* Chapter X, p. 79) until the convalescent stage is reached. It is desirable, as soon as the disease is diagnosed, to substitute a rubber mattress of the " Sorbo " type—which is far superior to the old air or water bed. Hardening of the skin with methylated spirit and drying afterwards with a dusting powder is a measure which must be carried out daily from the beginning of the illness.

Oral hygiene is of the utmost importance. Frequent cleansing of the mouth, tongue, teeth and lips is essential. Diluted glycerin and thymol (B.P.C.) is a suitable application.

B. DIET.—The general principles of the diet are laid down in Chapter XI. It is necessary to make a clear distinction between fluids contained in the diet and fluid given in the form of water or one of the modifications described under *Onset Diet* (Chapter XI), since the patient must drink at least 3 pints

of water per diem. Fruit juice, especially orange juice, is essential and may be given in drinks with glucose. Every patient must be considered individually in relation to the severity of the attack. It is generally agreed that an onset diet consisting entirely of milk is undesirable ; the patient comes to loathe the sight and taste of milk, which, moreover, tends to cause dyspepsia, distension and constipation. Nevertheless, milk or milk modifications must constitute the basis of the diet and, in one form or another, the patient should consume at first two pints of milk, gradually increased to three pints in the twenty-four hours. The stools must be watched for the presence of undigested curds, and the abdomen examined daily for the occurrence of distension. Either event is an indication that the milk should be diluted, peptonised or citrated, or given for a time as whey.

Enteric fever is a protracted febrile illness in which it is important to change to a *continuation diet*, with its higher calorie content, as soon as the intestinal conditions permit, and, thereafter, similarly to the *recovery diet* (Chapter XI). Articles likely to produce irritating intestinal residues, *e.g.*, cabbage, should be avoided.

Alcohol forms no part in the dietary and should not be regarded as a routine addition. There is no doubt that the prodigious quantities of this drug, which it was customary to order, were entirely unnecessary and harmful. Nevertheless, alcohol, prescribed at the right time, has saved the lives of many enteric patients. If the heart is flagging or the patient appears to be entering upon the typhoid state, small doses of dry champagne may tide him over a critical stage. If vomiting is troublesome, dry champagne may be the only form of alcohol which is retained.

C. SPECIFIC THERAPY.—*Specific Antiserum.*—From time to time specific antisera have been tried in the treatment of *typhoid* fever and found wanting. Recently, however, serum therapy has entered upon a new phase as the result of the use of a serum devised by A. Felix (1935). According to Felix, virulent strains of *Bact. typhi* (Vi-strains) produce a Vi-antigen ; the effect of this antigen is to make O-antigen resistant to the O-antibody. Therefore an effective therapeutic serum must contain Vi-antibody, and Felix's serum contains both.

Favourable effects upon toxæmia have been reported. The Lister Institute advised for adults three doses of 33 c.c. of concentrated serum of high potency. Children should receive half this dosage. To be effective the serum must be given early and in full doses irrespective of the severity of the attack.

In doses of 10 c.c. the serum may be used for the temporary protection of those who may have been, or may become, infected (*vide* Prophylaxis). It is to be noted that, so far, there is no specific serum for the *paratyphoid* fevers.

Vaccine Therapy and Non-specific Protein Therapy.—Vaccines, whether injected or given by mouth (Besredka's bile-vaccines), have not met with much favour in treatment. Non-specific protein therapy (protein shock) produced by the injection of minute amounts of peptone or sterile milk into a vein has produced dramatic results, but is not devoid of risk for an enfeebled patient. It is better avoided.

D. DRUGS.—Hitherto the treatment of enteric fever by drugs has been unsatisfactory. Antipyretics are undesirable; they may affect the heart. Pyrexia is best controlled by warm or tepid sponging (*vide* Chapter X). Intestinal antiseptics have proved of little value. As a urinary antiseptic in the treatment of bacilluria, hexamine has had a measure of success.

Recently we have had an opportunity of treating a series of cases of *typhoid* fever with two of the sulphonamide group of drugs, viz., sulphanilamide and sulphapyridine. A tentative opinion may be expressed that these drugs, particularly sulphapyridine, are capable of controlling the bacteræmia, and thus of moderating and shortening the illness. They must be given in full doses for the first few days, disregarding cyanosis. The exhibition of the drug selected should be controlled by (*a*) differential white blood counts at short intervals, and (*b*) repeated blood cultures. Sterility of the blood culture is an indication to reduce the dosage rapidly, or perhaps to withdraw the drug entirely.

The precautions enjoined in Chapter X should be borne in mind.

Cardiac Stimulants.—As already mentioned, used for this specific purpose in an emergency, dry champagne in small doses, repeated, may tide the patient over a critical stage. The ordinary cardiac stimulants are of little value. If it is mechanically feasible, intravenous glucose (25 to 50 gm. in a 50 per cent. solution of sterile normal saline) is a most valuable remedy. It may be possible to give glucose (5 per cent.) continuously by the drip method; if so, this is preferable to a single large intravenous injection.

Sedatives.—Restlessness and sleeplessness may be controlled by bromides and chloral. Delirium, if violent, may necessitate hyoscine. In hæmorrhage, morphine may be essential if a starch and opium enema proves ineffective or the hæmorrhage is severe. Opinion as to the advisability of transfusion is divided.

E. SURGICAL PROCEDURES.—*Perforation* necessitates immediate laparotomy and the rapid closure by purse-string sutures of the perforation or perforations. Complications such as acute suppurative cholecystitis or appendicitis demand the appropriate surgical treatment.

Prophylaxis.—1. **General Measures** (see Chapter XXVII, p. 332).—The security of the community against enteric fever depends primarily upon a pure water supply. A supply ordinarily pure, may by some accident become contaminated with enteric group organisms and so initiate an epidemic. The main danger arises from the existence of carriers (*q.v.*) whose excreta may by some mischance enter the water supply. These dangers are beyond the direct control of the clinician, but given early information that cases of enteric fever are occurring in the locality, he can do much if he regards water and milk as *prima facie* suspect, and advises wherever and whenever opportunity offers the boiling of all drinking water and all water used for the washing of cooking utensils, and the *efficient* pasteurisation or the boiling of milk.

Pending the investigations and precautions of the sanitary authority, the clinician will thus have enjoined elementary preventive measures against the two chief vehicles of infection, viz., water and milk.

2. **Carriers.**—In this country and others where in general the purity of the water supply is above suspicion, carriers remain as the chief reservoirs of infection, especially if they handle foodstuffs.

Prior to the *release* of an enteric fever patient it is customary to secure at least two or preferably three consecutive negative cultures from the stool and the urine, an interval of three to five days elapsing between the collection of specimens. In the great majority of cases bacteriological clearance is obtained by the time convalescence is complete, but in a variable percentage of cases, estimated as from 2 to 5 per cent., the patient continues to excrete, regularly or intermittently, enteric group organisms in the fæces or urine for long periods. The detection and treatment of chronic enteric carriers is therefore of the utmost practical importance.

The subject has been reviewed exhaustively by C. H. Browning and his collaborators (*Medical Res. Coun. Spec. Rep.*, Series No. 179, 1933), and what follows is based largely upon their monograph.

Carriers may be divided into (1) *temporary*, those who excrete the organisms for short periods during or after convalescence: if this period extends to six months after the

acute attack, the carrier state is likely to become (2) *chronic*, and if it extends to a year is unlikely to clear spontaneously, but, on the contrary, to become *permanent*.

Habitat of Organisms.—Carriers are divided primarily into *fæcal* (intestinal) and *urinary* excretors. Occasionally the organisms may be discharged from abscesses or sinuses. The fæcal excretors may be divided into (i) *biliary* carriers (gall-bladder, liver or bile-ducts), and (ii) true *intestinal* carriers, the focus being in the gut. These are much more uncommon than biliary carriers, but, as Browning points out, their recognition is important since a proportion of failures to obtain cure by cholecystectomy may be due to the patients being true intestinal carriers.

Biliary Carriers.—It has been estimated that the proportion of female to male carriers is four or five to one. Children rarely become chronic carriers. The typical carrier is "a married woman of thirty years of age and upward," *i.e.*, those who are the likely subject of gall-stones, and in fact chronic cholecystitis with or without gall-stones has been found in a high proportion at operation. On the other hand, naked-eye changes may be very slight or absent.

Urinary Carriers.—Bacilluria, as already noted, is of frequent occurrence during the attack. It may persist for days or weeks or may become permanent. Chronic urinary carriers may be of either sex. Intermittency tends to be more marked in urinary than in intestinal (biliary) carriers. The urine may remain free from organisms (which may be derived from a suppurative focus in one kidney only) for intervals of months.

Other Foci.—Browning and his co-workers record the recovery of enteric group organisms from the suppurative or necrotic lesions of post-enteric perichondritis, periostitis and osteomyelitis: from the pus of subcutaneous abscesses and otitis media. They have also been isolated from the tonsils of convalescents, and it has been suggested that "saliva infection" (C. M. Smith) from such persons may be the source of some outbreaks.

Detection of Carriers.—So far as the clinician is concerned, the detection of carriers is confined to the collection of suitable specimens for laboratory examination, and the following practical points may be mentioned:

(i) It is important to secure a soft or fluid stool, and this may be achieved by giving a purge, such as calomel, overnight and a saline in the morning. If it is not

possible for the stool to be examined speedily, it should be emulsified with a mixture of 30 per cent. glycerin and 0·6 per cent. sodium chloride solution. This prevents the overgrowth of coliform organisms.

(ii) *Widal tests* as ordinarily performed are not reliable in the detection of carriers since Browning and his collaborators found that carriers not infrequently yield negative reactions ; but Felix has emphasised the value of the detection of Vi-agglutinins. Bensted has found Vi-antibodies in the serum of the majority of *permanent* carriers, but in only 50 per cent. of *temporary* and *convalescent* carriers.

Disposal of Carriers.—In England and Wales, except that no recognised carrier may engage in a trade involving the handling of foodstuffs, there is no power to insist upon his or her isolation. Any measures taken must be with the acquiescence of the patient.

Treatment of Carriers.—Since methods other than surgical have hitherto proved unsuccessful, or at least unreliable, in the treatment of carriers, it suffices here, merely to enumerate them, viz., intestinal antiseptics, adsorbants, cholagogues, vaccines, acidophilus-milk, X-rays. It may be added, however, that success in the treatment of obstinate bacilluria has been obtained with sulphonamides, and this drug should certainly be tried with the usual precautions.

Hitherto surgical measures have yielded the best results. They comprise the removal of the focus of infection, whether this be in the gall-bladder, the kidney, or some non-visceral lesion such as a bone abscess. The patients must be good surgical risks, and the severity of cholecystectomy in the elderly must be borne in mind. B. B. V. Lyon (1932) records success from biliary drainage. (It may be that sulphonamides will prove less formidable substitutes.)

Vaccine Prophylaxis: T.A.B. Vaccine.—Prophylactic vaccination against typhoid was introduced by Almroth Wright in 1896. At first vaccines of *B. typhi* alone were employed, but nowadays a mixed vaccine of typhoid and paratyphoid A and B (T.A.B.) is invariably used. (In the East this is not uncommonly combined with cholera vaccine (T.A.B.C.).)

Dosage.—Two injections are given at intervals of five or seven days : the first injection usually consists of 0·5 c.c. of vaccine, the second of 1 c.c. In children these doses may be halved. In 1 c.c. of vaccine are contained *Bact. typhi*, 1000

million; and of *Bact. paratyphi A* and *B*, 750 million each. Local and transitory general reactions may follow. Protection is afforded for a year, and if the necessity then still exists, as in continued residence in the East, inoculation should be repeated. It is unnecessary to add that those proceeding to countries where enteric fever is endemic should be inoculated before starting.

The value of mass inoculations with T.A.B. was abundantly demonstrated during the last war: even if full protection against attack was not afforded, the course of the disease in the inoculated was milder.

As a means of protection of troops and of individuals who are likely to be frequently at risk, the necessity for inoculation permits of no argument; nurses, for example, who are attending upon enteric fever patients should invariably be protected from the daily risks they run. Whether during an epidemic of enteric fever in a particular locality large-scale immunisation should be carried out is a matter of controversy, and it has been disputed as to whether those who are in potential danger of infection, *e.g.*, the inmates of a house where a case has occurred, should or should not be inoculated. The reason for hesitation is the possibility of coincidence of a negative phase with the invasion period of the disease. There is no doubt that this occurrence, which cannot be ruled out entirely, has been greatly overstressed.

There is a promising, but as yet unproved, means of temporary protection of familial "contacts" of *typhoid* fever, viz., passive immunisation by means of Felix's antityphoid serum (*q.v.*). If there is considered to be any contraindication to active immunisation with T.A.B., this method should be adopted as early as possible.

Besredka advocates the oral administration of bile-vaccines, but their use has not made very great progress.

Other Precautions.—1 *Flies.*—The house-fly is an important factor in the spread of enteric fever, and the greatest care must be taken to exclude flies from the sickroom or from any contact with utensils or dejecta.

2. *Dejecta.*—Before disposal, stools and urine must be treated for two hours with a disinfectant solution, and every precaution taken against contamination of the attendant's hands.

3. *Bedding and Laundry.*—The smallest fæcal or urinary stain on the sheet may be a source of infection for the nurse. All garments and bedding, before being laundered, must be steeped in a disinfectant bath for twenty-four hours.

4. *Crockery, spoons and other utensils* must be boiled after each meal.

5. The nurse's *nails* must be kept short, and on no account must she consume any meal without thoroughly scrubbing her hands, and never in the same room as the patient.

SUMMARY OF CHAPTER XXX

Enteric fevers include *typhoid* and *paratyphoids*.

Mode of Infection: Ingestion of water, milk or food infected usually by carriers.

Clinical Manifestations: Pyrexia (staircase rise, continued infastigium, decline by lysis), diarrhœa or constipation, splenomegaly, toxæmia (if profound—typhoid state).

Diagnostic Aids:

Blood culture.

Blood count (leucopenia).

Bacteriological: fæces and urine.

Serological: for H and O agglutinins, particularly a rising titre.

Complications: Hæmorrhage, perforation.

Prophylaxis: Active immunisation with T.A.B. vaccine.

CHAPTER XXXI

UNDULANT FEVER (*Brucellosis*)

(*a*) MALTA OR MEDITERRANEAN FEVER. (*b*) ABORTUS FEVER

DEFINITION.—Undulant fever is caused by the ingestion of strains of *Brucella*. In its typical form the disease somewhat resembles enteric fever, but sweats, nervous phenomena, arthritis and gross splenomegaly are characteristic additions to the syndrome. The disease derives its name from the alterations of febrile and afebrile phases which may continue for many months. Infections with *Br. melitensis* tend to be more severe than those caused by *Br. abortus*, or *Br. suis*. Abortus fever frequently lacks some of the above features; subclinical infections are also common. In each type diagnosis is confirmed by agglutination tests and by the isolation of the organism from the blood or urine. *Br. melitensis* is conveyed in raw goat's milk; *Br. abortus* in raw cow's milk, and *Br. suis* chiefly by handling the carcasses of infected pigs.

Ætiology.—(*a*) *Malta Fever*.—Marston (1859) wrote the first account of "Mediterranean or gastric remittent fever," and Hughes (1897) described the same condition under the names of Mediterranean, Malta or Undulant Fever. Bruce (1887) isolated the causal organism *Br.* (*micrococcus*) *melitensis*. Zammit (1905) and others showed that in Malta the disease was caused by drinking raw milk from infected goats. The use of boiled goat's milk resulted in a rapid drop in incidence among the forces in the islands. Nevertheless among the civil population of Malta undulant fever is still the commonest notifiable disease. In 1936 among a population of some 260,000 there were 873 cases with 52 deaths—a case-fatality rate of 6 per cent. This number of cases is stated (Ann. Rep. Chief Govt. M.O., Malta, 1936) to have been the lowest since 1927; the decreased incidence being ascribed either to a diminution in the diffusibility and virulence of the infecting agent, or to an increased resistance to the disease among a large proportion of the population, immunity being acquired as the result of high prevalence.

(*b*) *Abortus Fever.*—The identification of the *Bacillus abortus* of Bang, the cause of contagious abortion in cattle, with human cases of undulant fever led to the discovery that human abortus infections both clinical and subclinical are of world-wide distribution. *Br. suis*, which occurs in the pig but which is transmissible to cows and pathogenic for man, has also been responsible for many outbreaks of like character, chiefly among slaughterers. *Br. abortus* is usually conveyed in raw milk, but infected animals or their excreta may infect farm hands, milkers, slaughterers or veterinary surgeons. After recovery from contagious abortion the cow's milk may continue to secrete the organism for long periods, *i.e.*, the animals become carriers. Direct infection of one human being by another has not so far been recorded. There is no particular *seasonal incidence.*

Age and Sex Incidence.—Although the disease is mainly conveyed by raw milk, young children are not those chiefly affected. Ohn (1937) found in Sweden that the age incidence of abortus infections per 100,000 of the population was 0·9 for those under five years and 15·2 for those between thirty and thirty-nine (*cf.* milk-borne enteric fever, Chapter XXX). Men between the ages of thirty to sixty provide twice as many cases as women and children. Ohn records that of 771 cases of abortus fever 36·6 per cent. occurred in women.

Dalrymple-Champneys suggests that men *because* they consume less milk are apt to lose that immunity which women and children maintain by the regular consumption of infected milk. Paterson and Hardwick (1938), however, explain the small number of cases in children on the following grounds: (i) many cases are not recognised; (ii) pasteurisation is successful in killing any organisms in the milk supply; and (iii) *Br. melitensis* and *abortus* are but mildly pathogenic. Champneys considers that subclinical infections may account for the apparently low incidence of the human disease in spite of the wide prevalence of contagious abortion in cattle. In 78 of 83 cases investigated by the same observer the patients were in the habit of drinking raw milk, whereas only 8 had had contact with bovines and, of these, 3 had drunk raw milk as well.

Walker Hall (1933) found that the serum of 7 per cent. of 590 healthy persons contained agglutinins for *Br. abortus*. On the other hand it has been shown in Denmark that two-thirds of the cases of undulant fever could be traced to contact with infected cattle.

Bacteriology.—*Br. melitensis* is a small non-motile, gram-negative coccobacillus which may occur singly or as a diplococcus. It is recoverable from the blood in the early stages of the illness (10 c.c. necessary for culture), from the urine and, post-mortem, from the spleen. *Br. abortus* and *Br. suis* can only be distinguished from *Br. melitensis* by absorption of agglutinins.

Blood Picture.—There is usually leucopenia, as in enteric fever. The polymorphs are reduced and there is a relative lymphocytosis.

Incubation Period.—The incubation period may range from six to twenty days ; a period of fourteen days is common.

Clinical Features.—(*a*) UNDULANT FEVER caused by *Br. melitensis* tends to be more severe than the disease caused by *Br. abortus*. Sheldon Dudley has pointed out the tendency for ships' companies to suffer from a single definite clinical type. Bassett Smith enumerated five types of *Br. melitensis* infection :—

(i) *Ambulant :* symptoms mild or absent. Since the organisms are excreted in the urine, ambulant patients are potentially dangerous as *carriers*.
(ii) *Mild :* the illness lasts about a fortnight and may be mistaken for *paratyphoid fever* (*q.v.* Chapter XXX).
(iii) *Ordinary :* this type is described below.
(iv) *Malignant :* signalised by hyperæmia and toxæmia ; usually proves fatal.
(v) *Intermittent :* hectic fever, sweats and wasting. Bronchopneumonia is not uncommon in this type and the condition is liable to be mistaken for *tuberculosis*.

Undulant Fever (*melitensis*) of Ordinary Type.

Invasion is insidious and the symptoms of fatigue, general malaise, aches and pains and anorexia closely resemble those of enteric fever. Nausea and palpitation are common early symptoms : the latter may persist for some time. Constipation is the rule. In this connection it should be remembered that constipation frequently occurs in the early stages of enteric fever—particularly paratyphoid fever. As in enteric fever, again, bronchitis may be marked in undulant fever.

A feature of the disease is the occurrence of transient but recurrent arthritis which " may affect any or almost all the joints, but particularly the sacro-iliac " (Dalrymple-Champneys). The nervous system, central and peripheral, is frequently affected : depression, irritability, insomnia, delirium, neuralgia and neuritis are common complaints. The spleen is markedly

enlarged and may reach the umbilicus, and in long-standing cases the liver also becomes enlarged.

The *temperature chart* is characteristic: it shows a variable number of waves of step-ladder ascent and descent separated by periods of apyrexia. Each pyrexial phase may last for a fortnight and be accompanied by profuse sweating; the apyrexial periods are shorter—persisting for perhaps a week or ten days. These alternating pyrexial and apyrexial phases recur on the average during three to four months, but may endure for a year.

Dalrymple-Champneys (1929) quotes Cantaloube that "the combination of sweating, aches, constipation, asthenia, undulant temperature and relapses is found more often in this than in any other disease and is sufficient to justify a diagnosis of undulant fever."

(*b*) ABORTUS FEVER.—The clinical picture of the "ordinary" type of melitensis infection is not applicable to abortus infections; the "ordinary" type of abortus infection is much less severe, and the characteristic undulant pyrexia with relapses may be altogether lacking. Many cases are of ambulant type, and in spite of the fact that the temperature between 4 P.M. and 8 P.M. may on successive days attain 103° F. or more, the patient feels comparatively well. In English examples of abortus infections, the onset of the illness has been either abrupt or insidious, and although lassitude, depression, anorexia, furred tongue and constipation have occurred as in melitensis infections, the illness as a whole has been less severe and of shorter duration, the average being ten weeks. The swinging temperature, dropping during the night, with the accompaniment of profuse sweats commonly occurs. Joint pains are absent or but little marked.

H. Cohen (1938) classifies five main clinical varieties of abortus fever, viz., (i) the classical undulant form, (ii) arthritic, (iii) abdominal, (iv) genital (orchitis), (v) "catarrhal jaundice" type (occasional occurrence of severe *early* hæmatemesis or melæna and *late* agglutination).

Undulant (abortus) Fever in Children.—In a series of cases described by Paterson and Hardwick (1938) the onset was abrupt with signs of nasopharyngeal infection in every instance. It was only the persistence of pyrexia which aroused suspicion. Fever usually ran an irregular course between 99° and 100·5° F. In one case the temperature reached 104° F. In some patients the bout of fever lasted for four months and in one instance for a year. In this series, the occurrence of headache, joint

pains or rigors was not observed. In two cases there was sweating and in one splenomegaly.

Diagnosis.—The diagnosis of undulant fever may present extreme difficulties. In this country the disease most likely to be confused is enteric fever (especially paratyphoid fever, *q.v.*). There is little doubt that if in the investigation of cases of "pyrexia of unknown origin" (P.U.O.), **agglutination tests** for *Br. abortus* in addition to those for enteric infections were invariably carried out, undulant fever would be diagnosed more often than it is. But the titre of agglutination is important. Formerly a titre of 1 in 80 to 1 in 100 was considered sufficient, but G. S. Wilson (1933) expresses the opinion that "the only satisfactory means is to take the agglutination reaction in conjunction with the patient's clinical condition; a titre of 1 in 1,000 is so unlikely to be due to a latent infection that it is almost always justifiable to refer the patient's condition to infection with *Br. abortus*." He adds that "latent infections in this country causing titres of 1 in 100 or over are uncommon, except in, *e.g.*, slaughterers. In the normal population of London, brought up largely on pasteurised milk, latent infections seemed to be exceptional, and a titre of 1 in 80 or over in the presence of pyrexia of unknown origin is strongly suggestive of *Br. abortus* infection." In Paterson and Hardwick's series in children (*vide supra*) agglutination was positive in every case to a titre of 1 in 500 or higher.

Blood culture may be successful in the early stages of the attack and the organism may also be recovered from the *urine*.

Skin Test—Brucellin.—The intradermal injection of an antigen prepared from *Br. melitensis* or *Br. abortus* may produce a local area of erythema in twenty-four hours. Since this "positive" result may occur in subjects whose serum fails to agglutinate the organisms, the test, in the absence of confirmatory evidence, cannot be regarded, in its present form at least, as reliable.

Prevention.—The prevention of undulant fever necessitates (i) the elimination of infected animals from herds by means of agglutination tests, and (ii) the *efficient* pasteurisation of milk. Pasteurisation at 145° to 150° F. for thirty minutes definitely kills *Br. melitensis* and *abortus* (G. S. Wilson, 1933). The nursing precautions to prevent the spread of infection are those enjoined for enteric fever (*vide* Chapter XXX).

Treatment.—Until recently treatment was chiefly symptomatic and not very effective. Evidence is accumulating in

favour of the sulphonamide drugs and several observers have noted a definite effect upon the duration of the disease. The dosage should be based upon the scheme suggested in Chapter X, p. 83, for moderately severe or mild infections. Caution in dosage is necessary because of the occurrence in patients suffering from undulant fever of leucopenia. This, of course, enhances the possibility of agranulocytosis if the drug is long continued. Frequent white-cell counts are desirable, especially in the elderly. If sulphanilamide is for any reason contraindicated, *e.g.*, idiosyncrasy, *fouadin* (a compound of antimony and pyrocatechin sulphonic acid) may be injected intramuscularly. The dosage advised is 1·5 c.c. on the first day, 3·5 c.c. on the second day and then 5 c.c. on alternate days afterwards. In female patients the maximum daily dose should not exceed 4·5 c.c. Favourable results have been recorded in both *melitensis* and *abortus* infections from the injection of fouadin. A measure of success has been claimed for vaccines and for non-specific protein shock (T.A.B.). Intestinal antiseptics, such as salol, and antipyretics, which tend to depress the heart, have no real value.

SUMMARY OF CHAPTER XXXI

Cause : *Br. melitensis* (in goat's milk) ; *Br. abortus* (in cow's milk) ; *Br. suis* (in pig's carcasses).

Chief Clinical Types : Ordinary ; mild ; subclinical.

Symptoms : Resemble enteric with marked sweats, nervous symptoms, arthritis, splenomegaly, alternating febrile and afebrile phases.

Aids to Diagnosis : Agglutination tests, blood culture, and culture from urine.

Prevention : Elimination of infected animals ; pasteurisation of milk.

Treatment : Sulphonamide and fouadin.

CHAPTER XXXII

PSITTACOSIS

DEFINITION.—Psittacosis is a virus disease of parrots and budgerigars or love-birds. It is transmitted to human beings through handling infected birds. Human outbreaks of parrot disease have occurred abroad from time to time. In this country, during the first half of 1930, some one hundred and twenty-three cases were diagnosed. This outbreak caused the issue of the Parrots (Prohibition of Imports) Regulations, 1930, and the prompt cessation of further human cases.

Infected parrots, commonly freshly imported, are not always obviously out of condition. The bird may be incubating the disease. But the parrot or love-bird actually suffering from psittacosis is listless and the plumage is rough and dirty. The bird has diarrhœa, the excrement may contain blood, and there is a discharge from the eyes and nose. Post-mortem signs are gastro-enteritis and possibly pneumonia. The excrement, discharges, and feathers so soiled are infective.

Bacteriology.—The *B. psittacosis* of Nocard, synonymous with *B. œrtrycke*, is *not* the causal organism of the disease. This has been shown by S. P. Bedson to be a filterable virus.

Laboratory Diagnosis.—1. SUSPECTED BIRDS.—Laboratory Diagnosis (see *Min. of Health Reports on Public Health and Med. Subj.*, No. 80, 1937). Special precautions are necessary in handling the pathogenic and dangerous material. Suspected birds should be asphyxiated at once and then soaked in lysol and wrapped in muslin or wool similarly soaked. Suspected living birds must never be transmitted for examination.

2. SUSPECTED HUMAN CASES.—(1) *Blood* obtained within first four days of the illness may contain the virus, but it is nearly always absent after this. The blood is inoculated into mice.

Complement-fixation may be obtained with the blood of convalescents.

If obtained early, sputum may contain the virus, and the same applies to pleural fluid.

(2) *Autopsy.*—The virus quickly dies out, and since death occurs late in the disease it is unlikely to be recovered at autopsy ; the virus is most likely to be recovered by pneumonic puncture of the lung, from pleural or pericardial effusions, or the liver and spleen.

" The commonest form in which the virus appears in smears from infected exudate, etc., is that of a minute coccus (0·25 μ) diffusely scattered . . . or in pairs or short chains. . . . The virus particle grows within the cytoplasm of susceptible cells and these become colonies. In all psittacosis infections the essential lesion is the invasion and destruction of the reticulo-endothelial system " (see *Min. of Health Rep.*, No. 80).

Clinical Features.—A patient suffering from psittacosis can infect another by contact. Adults are more commonly infected than children, both sexes being equally affected. The *incubation period* varies from four to sixteen days ; ten days is usual.

Human psittacosis bears considerable clinical resemblance to an enteric group infection. Invasion is more abrupt, however, and is sometimes attended by rigors. Headache, general aches and pains, nausea or vomiting are common manifestations ; sore throat frequently and epistaxis occasionally occur. Prostration is early and marked, and ultimately the patient sinks into the typhoid state. The temperature chart, too, is similar to that of an enteric group infection ; bradycardia is usual.

Although gastro-intestinal symptoms such as furred tongue, anorexia and constipation—which is much commoner than diarrhœa—occur, the outstanding clinical feature is the involvement of the lungs. There is in many cases a harsh, dry cough which may be paroxysmal and painful and productive of little or no sputum. Examination of the lungs shows broncho-pneumonia, and is characterised by daily changes in the physical signs as fresh areas are involved.

Rose spots have been reported in a few cases. In a fatal case in the personal experience of one of us, in which a retrospective diagnosis of psittacosis was confirmed, the patient was notified as suffering from scarlet fever. She had a generalised scarlatiniform rash and in many respects her illness resembled the septic type of scarlet fever, terminating in broncho-pneumonia—notable for the rapid alterations in the pulmonary physical signs.

Prophylaxis.—The extreme danger of handling infected birds, their cages or articles soiled by their excrement must be emphasised, although the stringent application of the regulations has reduced the risk of their importation into the

country to negligible proportions. The nursing of human psittacosis demands for the safety of the attendants the same precautions as those observed in the management of cases of enteric fever.

Treatment is purely symptomatic.

SUMMARY OF CHAPTER XXXII

A virus disease of parrots and love-birds transmissible to human beings.
Gastro-intestinal symptoms resembling enteric fever and respiratory signs of broncho-pneumonia.
Prophylaxis: administrative measures; personal precautions.

CHAPTER XXXIII

INFECTIVE JAUNDICE

I. WEIL'S DISEASE. II. EPIDEMIC CATARRHAL JAUNDICE

I. WEIL'S DISEASE

(*Spirochætosis icterohæmorrhagica* ; spirochætal jaundice ; icterohæmorrhagic jaundice)

DEFINITION.—A severe disease caused by the entrance, usually through the abraded skin, of the *Leptospira icterohæmorrhagiæ* contained in mud or water contaminated by the urine of infected rats. It is characterised by an abrupt onset with headache, vomiting, pyrexia, conjunctival injection and prostration, followed in a few days by jaundice, enlargement and tenderness of the liver and mucous and cutaneous hæmorrhages.

Ætiology.—The disease was first described by A. Weil (1886) and shown by Inada and Ino (1914) to be caused by the *Leptospira icterohæmorrhagiæ.* Rats and other small rodents become infected, but not necessarily ill, and act as vectors, the organism being excreted in the urine. It can be recovered post-mortem from the kidney and gut. Human outbreaks have occurred among coal miners, sewage workers, fish cleaners, and also among children bathing in infected water. During the Great War the disease affected troops in the trenches.

Mode of Infection.—The organism enters through abrasions of moist or sodden skin ; through the bites of infected animals ; or as the result of swallowing infected water. It can apparently penetrate the healthy conjunctiva.

Sex Incidence.—As might be expected in an occupational disease, men are more frequently infected than women, except in the case of fish cleaners among whom the sex incidence is equal (Smith and Davidson, 1936).

Mortality.—The fatality rate varies greatly. In Japan, where the disease is endemic, epidemic and severe, fatality rates of 40 per cent. have been reported. During the last war

the rate was from 2 to 3 per cent. An average rate is 10 to 15 per cent. Alston and Brown (1937) point out that by serological methods many unjaundiced clinical infections can be detected and these correct the rather high fatality rate based upon jaundiced cases only. Among 143 obvious clinical cases occurring in the British Isles in three and a half years they found that the case-fatality rate was 15 per cent., although in hospital-treated cases it may be as high as 50 per cent.

Bacteriology.—The *Leptospira icterohæmorrhagiæ* is a slender, cylindrical, highly flexible filament with very tightly wound and rather shallow spirals. At each extremity it is bent over in the form of a hook (Alston and Brown). Fresh preparations examined by dark-ground illumination show active movement. The organism can be seen in smears stained with Giemsa, and can be cultivated in Noguchi's medium. It can be isolated from the patient's blood during the first few days of the attack, and later, about the tenth day, from the urine.

Agglutinins are produced and serve as a diagnostic test. They begin to appear after the first week. The macroscopic test of Smith and Tulloch (1937) is recommended. Complement-fixation is also demonstrable, and by some is regarded as reliable as the agglutination test.

Blood Picture.—Leucocytosis with an absolute and relative increase in the polymorphonuclears occurs and is an important diagnostic point (*cf.* epidemic catarrhal jaundice, *infra*). The monocytes may also be increased, but there is no change in the absolute lymphocyte count. Hence the lymphocyte-monocyte ratio is greatly altered. The normal 85 : 15 may become 60 : 40 or even 50 : 50 (A. F. Sladden, 1939).

Incubation Period.—The usual period is from seven to thirteen days with limits of from four to nineteen days (Alston and Brown).

Clinical Features.—The onset is abrupt, with rigors or convulsions, pyrexia (102° to 104° F.), headache which is usually frontal, muscular twitchings and tenderness, conjunctival injection and, frequently, herpes labialis. Prostration is severe. This stage of invasion, during which the organism is circulating in the blood stream, is succeeded by the stage of jaundice, which commences upon the fourth or fifth day, and is associated with enlargement and tenderness of the liver and also, occasionally, the spleen. Jaundice deepens progressively up to the tenth day. Prostration increases and various hæmorrhages, particularly epistaxis and petechiæ, occur. Hæmatemesis, hæmoptysis and melæna are not uncommon. The urine contains albumen, casts and bile. After about the

tenth day the illness abates and the temperature falls by lysis. Relapses are common. A return of pyrexia of intermittent type may occur and last for as long as three weeks. This secondary fever is not attended by the other symptoms mentioned. Thus the whole attack may last for five or six weeks (Smith and Davidson). Second attacks, as distinct from relapses, have been recorded by some observers. The organism may be recovered from the blood for some weeks after the attack.

ATYPICAL FORMS.—Atypical forms without jaundice occur as do subclinical infections. Alston and Brown (1935) found agglutinins and protective antibodies in the blood of nine out of forty-five London sewer workers who were in good health and with no history of jaundice. Smith and Davidson report similar findings among fish workers in Aberdeen.

Pyrexial or apyrexial attacks with jaundice and hæmorrhagic nephritis; an illness of typhoid-like character with splenomegaly and nephritis but *without* jaundice; and febrile attacks without jaundice or nephritis but with conjunctival injection have been reported. Influenzal and meningeal types (simple spirochætal meningitis) also occur. In these atypical forms diagnosis may only be possible by finding the organism in the blood or cerebrospinal fluid or by agglutination tests. F. Murgatroyd (1937) records a prolonged case of Weil's disease which was associated with meningitis of a progressive type, the first evidence of meningeal invasion being observed four months after the onset of the illness. The diagnosis was made by finding the leptospira in the cerebrospinal fluid and in the urine. Murgatroyd advises that leptospiral infection should be considered in any obscure case of meningitis or, indeed, any case of obscure pyrexia.

Diagnosis.—The clinical diagnosis may be confirmed by: (i) intraperitoneal injection of 5 c.c. of the patient's blood obtained during the first five days of the disease into guinea pigs. The animal dies about the tenth day after inoculation and leptospiræ may be obtained in great numbers from the liver, spleen and kidney. Sometimes the organism is demonstrable in stained smears of the patient's blood. (ii) Culture from the urine after the tenth day of the attack. (iii) Agglutination and complement-fixation tests after the first week.

These laboratory tests are largely retrospective, but should always be performed. Early Van den Burgh tests show very high degrees of bilirubinæmia and there is high saturation of the urine with bilirubin (Sladden).

The differential diagnosis between Weil's disease and

epidemic catarrhal jaundice will be discussed after the description of that condition (*vide infra*).

Treatment.—Except for symptomatic treatment, drugs have proved of little value. Glucose should always be given, and W. E. Rees (1939) believes intramuscular injection of calcium gluconate to be useful. Experiments are being made to discover a drug with specific action upon the leptospira, and various organic compounds of bismuth have been tried in infected guinea pigs. Immune serum prepared from rabbits has been used with success upon a small scale in human beings, and should be given, if available, in every case. Convalescent serum has also been employed.

Prophylaxis must consist chiefly in the destruction of rats, particularly in mines and sewers. Alston and Brown (1935) suggest the use of prophylactic vaccines in widespread outbreaks, or in the case of workers known to be exposed.

II. EPIDEMIC CATARRHAL JAUNDICE

Definition.—A mild disease probably caused by a filterable virus and affecting chiefly children. It is characterised by a gradual onset, with general malaise, slight pyrexia, nausea and lassitude, followed after three or four days by vomiting, upper abdominal pain, tenderness over the gall-bladder, and jaundice which attains its maximum intensity in from two to four days and may last for three weeks. In this type there are no complications and few deaths, but a more severe form occurs which is distinguished by some as infective hepatic jaundice—a different disease. Infection is conveyed by droplet spray as the result of close personal contact.

Ætiology.—Epidemic catarrhal jaundice was first described by E. A. Cockayne (1912), who distinguished the condition from Weil's disease. Some consider it to be the epidemic form of sporadic catarrhal jaundice. H. Barber (1937) suggests that most cases of catarrhal jaundice are really due to an acute hepatitis and should be called infective hepatic jaundice. Hurst and Simpson (1934) made a clinical distinction between true catarrhal jaundice and mild hepatic necrosis, but W. N. Pickles (1939) maintains that the two variations occur in the same epidemics and have the same epidemiological behaviour.

The **ætiological agent** is unknown, but is believed to be due to an ultramicroscopic virus. In favour of a virus causation have been adduced the long incubation period, the characteristic blood changes (*vide infra*) and the difficulty of transmitting the disease to lower animals.

Mode of Infection.—The available evidence goes to show that the disease is spread among close contacts by means of droplet spray. There is no evidence that animal vectors such as rats play a part. The clothing, hands or fomites soiled by the excreta of infected persons have been suggested as secondary sources of infection (Morgan and Brown, 1927). Infected swimming-bath water is a possibility (Glover and Wilson, 1931). Pickles (1939), however, is satisfied that personal contact is the only factor in the spread of the disease.

Seasonal Incidence.—Outbreaks have been most frequent during the autumn and winter.

Age and Sex Incidence.—Children of school age are those chiefly affected, and they frequently attend the same school. In an outbreak described by Glover and Wilson 20 per cent. of the patients were young adults, and adults of all ages may be attacked. The sex incidence is not characteristic, although in some outbreaks female cases have preponderated.

Mortality.—The case fatality is very low ; recovery is the rule.

Blood Picture.—There is an increase in the large mononuclears and transitional lymphocytes, but *no* relative increase in the polymorphonuclears (*cf.* Weil's Disease, *supra*).

Incubation Period.—The incubation period is considered by most observers to be long—from twenty to forty days (Booth and Okell) ; from twenty-six to thirty-five days (Pickles) ; from three to thirty-five days (Morgan and Brown) ; from three to four days (Glover and Wilson)—the long periods being ascribed to " missed cases."

It is believed by some that the disease is infectious in the later stages of the incubation period.

Clinical Features.—The onset is gradual. There is a period of general malaise, with headache, anorexia and nausea. The child is miserable and may be drowsy. In some outbreaks tonsillitis or nasopharyngeal catarrh have been noted at the onset. Epistaxis and conjunctival injection have also been inconstant features. The temperature rarely exceeds 102° F. Lisney (1937) noted that in some children a flushed face was associated with a normal temperature and most of his patients had bradycardia. These prodromata last for possibly three or four days and are followed by vomiting and complaint of pain in the upper abdomen. The gall-bladder is palpable and tender. At any time from one to four days after these acute symptoms jaundice may appear. It attains its maximum intensity in from two to four days, and may disappear in a

week or last for as long as three weeks. Lisney observed that when jaundice appeared the child felt better. In his series the conjunctivæ were first affected, and next the face, neck, arms, trunk and legs. Itching was intense; the fæces pale and the urine dark.

Hæmaturia is an occasional complication, but usually recovery is uneventful. Opinion is divided as to whether *severe* attacks of epidemic catarrhal jaundice are not really due to *infective hepatic jaundice,* which Hurst and Simpson (1934) believe to be quite distinct. Thus in the latter there are no prodromal pre-icteric symptoms, pale fæces and dark urine being passed immediately before the appearance of jaundice and the general symptoms of malaise, vomiting and pyrexia. Although the liver and spleen are enlarged there is no epigastric tenderness. Fatal cases of infective hepatic jaundice have shown hepatic necrosis at autopsy.

Relapses and *second attacks* of epidemic catarrhal jaundice are rare.

Differential Diagnosis. — Distinction has to be made from :—

(i) Infective hepatic jaundice, if this is recognised as a separate clinical entity (*vide supra*).

(ii) Weil's disease (*vide supra*).

(iii) The various types of jaundice in young infants, *e.g.*, *icterus simplex neonatorum* and *icterus gravis neonatorum* (*familial*), and acute and subacute yellow atrophy of the liver in children are unlikely to be mistaken for epidemic catarrhal jaundice. Some observers believe simple catarrhal jaundice to be the sporadic form of the epidemic type. Lisney, however, points out that whereas in the epidemic form an occasional bile-stained stool is passed, in simple catarrhal jaundice (obstructive) the stools are pale throughout.

Treatment.—This is simple : bed ; light diet with plenty of fluid, orange juice and glucose ; aperients—small repeated doses of calomel and salines. If jaundice is marked, sodium salicylate may be of value.

Prophylaxis.—Isolation should be maintained for two weeks. Pickles finds that after this period children may return to school without danger of spread to others. The real danger arises from those who have suffered attacks so mild that no medical attention has been called for. As a rule, school closure is not necessary.

The following table gives the chief clinical differences between Weil's disease and epidemic catarrhal jaundice.

TABLE XXIII

Weil's Disease	Epidemic Catarrhal Jaundice
Incubation : Seven to thirteen days.	Incubation : Twenty-six to thirty-five days.
Severe.	Benign.
Hæmorrhages, *e.g.*, epistaxis and petechiæ constantly present.	Occasionally slight epistaxis at onset. Hæmaturia in some.
Sudden, severe onset, rigors, great prostration, injected conjunctivæ.	Onset gradual and benign. Conjunctivæ frequently injected.
Liver enlarged.	Liver seldom palpable.
Frontal headache, twitchings, convulsions, tenderness of muscles.	Very slight headache. Marked nervous symptoms exceptional.
Initial fever of 102° to 104° and marked secondary fever.	Initial fever seldom more than 102°, and usually no secondary fever.
Jaundice appears on fourth or fifth day. Increases in intensity up to tenth day. Lasts about three weeks.	Jaundice appears on fourth to seventh day : reaches maximum in two to four days. May last three weeks, but usually disappears in a week.
Blood : Leucocytosis with absolute and relative polymorphocytosis.	*Blood :* Monocytosis ; *no* increase of polymorphonuclears.

(Modified from Morgan and Brown.)

CHAPTER XXXIV

EPIDEMIC LOUSE-BORNE DISEASES

I. EPIDEMIC TYPHUS. II. TRENCH FEVER.
III. EPIDEMIC RELAPSING FEVER.

INTRODUCTORY.—The three diseases described in this chapter are transmitted by the louse (*Pediculus humanus*). Thus they tend to become prevalent when infestation with lice is also prevalent, notably, therefore, in the environmental conditions imposed by war. Trench fever, as its name implies, is peculiar to life in the lines. Epidemic typhus and trench fever are caused by Rickettsia bodies, relapsing fever by a spirochæte. Epidemics of louse-typhus and louse-relapsing fever are not uncommonly concurrent, and when this is the case double infections frequently occur. Short of obviating the conditions under which the louse, infective or not, thrives, the prophylactic measure applicable to all three diseases is systematic disinfestation.

In this chapter the main stress is placed upon the clinical aspects of these louse-borne fevers, but it is necessary for medical officers, in both civil and military practice, in time of war, to have a sound knowledge of the biology and pathology of *P. humanus* and of the methods of its control.[1]

I. Epidemic Typhus

(*Exanthematic, European or Louse Typhus*)

Definition.—Epidemic typhus is caused by *Rickettsia prowazeki* conveyed from man to man by *Pediculus humanus*, the intermediate host. The disease is characterised by an abrupt febrile onset with early and severe constitutional disturbance, prostration, a macular rash which avoids the face and nervous manifestations. The attack ordinarily terminates by short lysis about the fifteenth day.

[1] See especially P. A. Buxton's monograph "The Louse," London, 1939, and the latest issue of the *Army Manual of Hygiene.*

Ætiology.—Epidemic typhus is the most important member of a group of fevers caused by species of Rickettsiæ (*vide infra*), and the only member of the group which is solely a human disease. It is conveyed by an ectoparasite, *Pediculus humanus*, whose only host is man. The other forms of typhus or typhus-like fevers are primarily epizootics, and with the possible exception of murine typhus, only occur in non-epidemic form in man.

H. Zinsser (1935) considers that true typhus comprises two main types, viz., epidemic, European or louse typhus, and murine (rat) typhus. Murine typhus is ordinarily transmitted from rat to rat by the flea, *Xenopsylla cheopsis* (or a rat-louse (Buxton).) This flea may also transmit the disease to man. Once so transmitted, according to Zinsser, it may be disseminated from man to man by *P. humanus*.

The following classification of the typhus group of fevers is modified from that of J. Megaw.[1]

TABLE XXIV

(After Megaw)

Typhus Fevers

	EPIDEMIC	EPIZOOTIC (*Non-epidemic*)			
Host	Man	Rat	Ground squirrel, dog, etc.	Mouse	Unknown
Vector (*Intermediate host*)		Flea	Tick	Mite	
Occasional host		*Man*	*Man*	*Man*	*Man*

Murine and other epizootic forms of typhus occur, *inter alia*, in the Mediterranean basin, the Malay States, and Japan, and their description should be sought in works on tropical medicine.

Epidemic Typhus is one of the major diseases of Eastern Europe, and in past wars has invariably assumed gravely enhanced importance either as concomitant or aftermath.

C. Murchison in his classical work "The Continued Fevers of Great Britain" (1862), remarks that "a complete history

[1] See J. Megaw in Leonard Rogers and Megaw, "Tropical Medicine," Third Edition, 1939, p. 182.

of typhus would be the history of Europe for the past three and a half centuries. . . . The history of typhus epidemics demonstrates their intimate connection between famine and distress. They have appeared during every variety of climate, season, and weather; famine and overcrowding have been the sole conditions common to them all."

The synonyms for typhus have been legion: famine, jail, camp, ship and hospital fever are among the most grimly suggestive.

When Murchison wrote, European typhus was endemic in this country. In Western Eire there are still a few endemic centres from which the disease is occasionally introduced by immigrants into the tenements of such ports as Liverpool and Glasgow. Mathieson and Leete (1924) described an outbreak of twelve cases of varying clinical types which occurred in Birkenhead in 1922, the infection presumably being introduced from abroad. Except for such fortuitous introductions, the disease is extinct in Great Britain. Eastern Europe and Russia are the main endemic centres and, as in the war of 1914-18, devastating epidemics may again scourge their destitute inhabitants and prisoners in internment and concentration camps. Refugees may spread the disease to countries ordinarily exempt. E. W. Goodall (1920) recorded that during the years 1916-19 typhus was endemic throughout Poland and over 430,000 cases occurred. F. G. Clemow (1921) pointed out that whereas before the Great War typhus was rare in Turkey, the disease, owing to the great influx of Russian refugees, became widespread during the winter months. In Serbia, too, very large numbers of cases occurred, these being ascribed to the internment of Austrian prisoners. It is noteworthy that although typhus was repeatedly introduced into France the disease did not spread in the army or among the civil population; an epidemic in Marseilles in 1919 was confined to prisoners of war. In the British army during the last war typhus occurred only on fronts where the disease was endemic. From personal experience, the disease among the troops in Mesopotamia was largely confined to accidental infections of stretcher bearers or ward orderlies by Persians or Kurds of the coolie class admitted to hospital with typhus.

Seasonal Prevalence.—In endemic centres, louse-typhus tends to be more prevalent during the months of cold weather. The huddling together of the destitute for warmth favours its transmission.

Age Incidence.—The disease occurs at all ages; infants and the very old may be attacked. Under abnormal conditions

the age incidence is obviously determined by the type of community at risk. The same statement applies to *sex incidence*.

Mortality.—Lethality increases with the age of the patient. Among children the fatality rate is low; 5 per cent. or less among recognised cases, whereas among those over fifty years of age the fatality rate may exceed 50 per cent. At all ages the fatality rates range from 15 to 20 per cent. in different epidemics.

Causal Agent.—Louse-typhus is caused by *Rickettsia prowazeki*. The precise nature of the Rickettsia bodies is not yet clear. Zinsser (1935) defines them as pleomorphic micro-organisms usually seen in short bacillary or diplobacillus form which may, according to environmental conditions, species of host or degree of crowding in cells, look like minute cocco-bacilli or appear as longer straight or curved filaments which approach in size the smaller bacteria. They are non-motile and Gram-negative and, in smears stained with Giemsa, exhibit a faint purplish tinge.

Intermediate Host. — The intermediate host or vector is *Pediculus humanus*, chiefly the body-louse (*P. corporis*), but sometimes the head-louse (*P. capitis*).

Transmission.—*R. prowazeki* is present in the blood of the patient during about the first ten days of the attack, and as Nicolle (1909) showed, is transmissible to chimpanzees.

A louse, having sucked the blood of the patient, becomes *infected* with Rickettsiæ but *not infective* for another human host until after a latent period of from seven to ten days. During this period the organisms proliferate in the mid-gut of the insect and *also* in the *epithelial lining* of the gut.

(*R. muricola* or *mooseri*, the organism causal of murine typhus, is also *intracellular*, whereas *R. quintana*, associated with trench fever (*vide infra*), is found only in the lumen of the gut and *not* in the epithelial lining (*vide* Buxton, "The Louse," p. 157).)

By the end of the latent period the epithelial cells and the lumen of the gut have become packed with Rickettsiæ and these are now passed in large numbers in the excrement of the insect. If the infective louse now bites another human host irritation is produced, and if excrement has been deposited upon the skin the host in the act of scratching inoculates himself with the causal organism of the disease. Transmission is not brought about by the *bite* of the louse but by the auto-inoculation of infective excrement. Dried louse excrement may contain living Rickettsiæ for many days, and there is

some evidence that the inhalation of such excrement is an exceptional mode of transmission (*cf.* trench fever). It has been stated that Rickettsiæ may penetrate the conjunctiva (*cf.* leptospira in Weil's Disease, Chapter XXXIII., p. 398. The infected louse dies shortly after it has become infective.

Pathology.—The characteristic histopathological lesion is a proliferative angeitis, the organisms being aggregated in the cytoplasm of the endothelial and mesothelial cells (Zinsser). Local necrosis of the vessel wall results, with the formation of "nodes" consisting of Rickettsiæ, cells of the vessel walls and white blood cells. These nodes are chiefly to be found in the vessels of the brain and skin. As to naked-eye appearances, the oft-quoted statement of C. Murchison (1862), based upon the performance of large numbers of autopsies, may be repeated here: "There is no lesion constant in, or peculiar to, typhus; the intestines never exhibit the peculiar lesions invariably present in enteric fever, and the mesenteric glands are not enlarged." Among the positive findings are petechial lesions in the skin, degenerative changes in the skeletal muscles and the myocardium, softening and congestion of the liver, spleen, pancreas and kidneys, bronchitic and hypostatic congestive changes in the lungs and small meningeal, cerebral and cerebellar hæmorrhages.

Blood Picture.—Accounts of the leucocyte picture are conflicting. According to J. D. Rolleston (1929), leucocytosis occurs from the beginning. It affects chiefly the polymorphonuclear cells, but, as in enteric fever, there is eosinopenia. Others have recorded leucopenia during the febrile period, the polymorphonuclears being normal or slightly diminished throughout the febrile and convalescent stages. There is, however, an increase in the lymphocytes with slight mononucleosis. The mononucleosis may be masked by a secondary polymorphocytosis towards the end of the attack as the result of septic complications (Nicolle and Conseil). The red cells and hæmoglobin content are increased. This contrasts with enteric fever in which there is hypochromic anæmia.

Stages of Typhus.—Attacks of typhus vary greatly in severity; in children they tend to be mild and atypical; in the elderly, severe and fatal. The clinical features presented in different epidemics are also variable, and in the same epidemic differing clinical types may occur. Nevertheless, there are certain outstanding characteristics in the symptom-complex. Murchison considered that the majority of attacks might be divided into more or less well-defined stages, viz., (i) *incubation*, (ii) *invasion*, (iii) "*nervous excitement*," (iv) *typhoid state*,

(v) *defervescence* and (vi) *convalescence*. Each of these stages is variable in duration and gravity, and transition from one to another may be ill-defined.

Incubation Period.—The most usual incubation period is from **twelve to fourteen days.** Periods as short as five or as long as twenty days are recorded. Owing to the fact that during the last two or three days of incubation the patient may feel unwell, this period is sometimes included as part of the stage of invasion, but the actual onset of the attack differs in character from these vague prodromata.

Clinical Features.—*Invasion.*—This stage lasts from the onset until the appearance of the eruption, *i.e.*, for four or five days. The *onset* is abrupt, the initial illness varying in severity from moderate general malaise of influenzal type to great constitutional disturbance. Shivering, pyrexia (102° to 104° F.), lassitude, severe frontal headache with pain over the eyeballs, tinnitus and vertigo, sore throat and slight cough, pains in the limbs and back are common. Anorexia and positive distaste for food are characteristic, but thirst is considerable. Epigastric pain or tenderness is sometimes a feature. More severe attacks may commence with nausea, rarely vomiting, a rigor or convulsions. In children, and sometimes in adults, a meningeal reaction may occur.

The face presents a dull red flush, not confined to the cheeks; the eyelids are heavy and swollen; characteristic is *conjunctival injection*. The expression is at first one of languor, but in a day or two the features appear heavy, dull and bloated. Insomnia is the rule, and such sleep as the patient obtains is broken by distressing dreams. Mental confusion and physical prostration are prominent symptoms. The pulse is disproportionately rapid and easily compressible. The temperature rises rapidly after the second day and may attain to 105° F., and, with but slight morning remissions, is maintained at a high level until defervescence. There may be a pre-critical rise. Respirations are moderately increased.

The *tongue* is large, flabby, possibly indented by the teeth, and covered by a thick white fur. The bowels are constipated; diarrhœa is very exceptional. Oliguria with albuminuria is usual. The *spleen* is enlarged in some cases.

These signs and symptoms continue until the appearance of the rash; on its appearance the patient's condition deteriorates, and with the completion of the eruption the illness enters upon the stage of "nervous excitement."

The *rash* in its early stage consists of pink macules varying in size from a pin's head to a lentil; they are just palpable

and at first disappear on pressure. In a day or two the lesions become dull red, cease to be palpable, and finally turn to slate-blue or grey before disappearing. In the centre of some of the macules *petechiæ* may occur or the whole lesion may become petechial.

The macules first appear upon the anterior folds of the axillæ and upon the abdomen, next upon the chest and back, the shoulders and limbs. They may first occur upon the backs of the hands and some maintain that the palms are characteristic sites.

With the rarest exceptions the rash of epidemic typhus *does not invade the face.* (This statement does not apply to some of the endemic forms.) Murchison insisted that the rash *does not appear on crops* (*cf.* enteric fevers).

Following the eruption of macules, paler "subcuticular" lesions, some of which may be as large as a shilling, appear between the macules and produce an effect of marbling. These subcuticular lesions are by no means constant. In addition, ecchymoses may form upon the skin of dependent parts. Branny desquamation, especially evident from the twelfth to the fifteenth day, has been observed by some.

It is important to note that, in children especially, the eruption may *never* appear, or may be confined to a few macules upon the chest.

"*Nervous Excitement.*"—The stage of invasion lasts about a week and then the clinical picture alters. The dull stuporose patient becomes delirious. The delirium of typhus may be violent but more usually is of a quiet muttering type. Prostration increases; the facies becomes more bloated. The tongue is now dry and brown, and on protrusion, if this is possible, shows fine tremors. The breath is offensive. Sordes collect. This stage of nervous excitation lasts for three or four days and the patient then passes into the *typhoid state* (see Chapter V, p. 38). The special features of this state in typhus are: (i) horrific *dreams*, sometimes of an occupational nature; (ii) the *tongue*, which becomes shrivelled, owing to the wasting of the intrinsic muscles, nearly black, tremulous, and frequently impossible of protrusion; and (iii) the *odour* of the patient's body which has been compared to that of mice or boot-blacking, but which Murchison considered to be *sui generis*.

The patient may sink into a condition of coma vigil and succumb, or survive and, more or less abruptly, pass into the stage of *defervescence*. After a quiet sleep "he awakes another man"; the temperature has fallen, the skin has become

moist, and the pulse slow; the tongue has cleaned and the bowels are moved; mental clearness returns and the patient enters the stage of *convalescence*.

Relapses during the course of the illness do not occur (*cf.* enteric fever, trench fever and relapsing fever), but *Brill's disease* is believed by Zinsser to be possibly a *late recrudescence* of epidemic typhus in persons who before immigration to the United States have suffered from louse-typhus. Brill's disease is therefore to be considered as a mild type of epidemic typhus which has become established endemically in cities with large immigrant populations (Zinsser). It is important to observe that Brill's disease is *not* transmissible by lice and therefore does not become epidemic.

Second attacks of epidemic typhus, *i.e.*, as the result of re-infection by lice, are rare but undoubted. Murchison himself had two attacks at an interval of ten years.

Complications and Sequelæ.

NERVOUS SYSTEM.—Violent *delirium* may be a troublesome complication. *Melancholia* is an occasional sequel. *Peripheral neuritis*, *cerebral hæmorrhage* or *thrombosis*, *bulbar lesions*, *oculomotor palsies*, *optic neuritis*, *choked disc* and *nerve deafness* have been recorded.

CIRCULATORY SYSTEM.—*Myocardial degeneration* is not uncommonly the cause of death. *Thrombosis* of the *femoral vein*, *gangrene of the feet* and *thrombosis* of the *intestinal arteries* with resultant *intestinal gangrene* may occur.

RESPIRATORY SYSTEM.—*Bronchitis*, *bronchopneumonia* and *hypostatic congestion* are all of common occurrence. *Ulcerative laryngitis* may be a sequel.

DIGESTIVE TRACT.—*Parotitis* is common. In about a quarter of the cases of parotitis, suppuration occurs. Intestinal lesions are rare.

MUSCLES, BONES AND JOINTS.—Patches of Zenker's degeneration affecting large muscles may occur. *Costal osteochondritis* and *spondylitis* (similar to "typhoid spine") have been recorded.

Diagnosis.—(i) *Clinical.*—During the first three or four days of the attack, *i.e.*, before the appearance of the rash, such conditions as influenza, apical pneumonia, relapsing fever, trench fever, mosquito-dengue, cerebrospinal fever, the prodromal stages of smallpox and measles, malignant tertian malaria, or enteric fever may be suspected. The rapid onset with sharp rise of temperature, lacking a step-ladder character, and the disproportionate tachycardia are quite different from the insidious mode of invasion which characterises enteric

fever. But before the appearance of the rash it may be impossible to make a diagnosis of typhus on purely clinical grounds. Previous vaccination or re-vaccination may serve to exclude smallpox, and the absence of Koplik's spots is against a diagnosis of prodromal measles. Later, the distribution, character and evolution of the rash, which invades the face first in smallpox and measles but avoids it in typhus, are diagnostic. The early prostration and early manifestation of nervous symptoms are, together with the dulled mentality and the flushed and bloated facies, characteristic of typhus. Contrast the alert mental state and the grey, fatigued and drawn facies of the prodromal stage of smallpox.

(ii) *Accessory Aids.*—As in all obscure toxic states, blood films, repeated complete red and white blood counts, hæmoglobin estimations, blood cultures and, if there is a meningeal reaction, lumbar puncture, are essential in order to exclude some at least of the conditions mentioned above.

Thus relapsing fever and malaria may be excluded by an examination of stained blood films alone, provided these have been taken during the pyrexial stage. Blood culture is likely to be positive in enteric fever and cerebrospinal fever. If there is a meningeal reaction, the cerebrospinal fluid in typhus is under pressure but is clear; it shows an increase in lymphocytes and a diminution in chlorides. The fluid reduces sugar. Contrast these characters with those shown in Table XVIII (p. 283).

The *diazo reaction* (see Chapter XXX, p. 379) is stated to be invariably and markedly positive at the *onset* of typhus (*cf.* enteric fever).

Weil-Felix Reaction (or *Wilson-Weil-Felix Reaction*).—From the beginning of the second week, or a day or so earlier, the serum of a patient suffering from louse-typhus is found to agglutinate suspensions of the *B. proteus X.* 19 (O-cultures (*O.X.* 19) being used).

The *B. proteus X.* 19 was originally isolated from the urine of typhus patients. It is, of course, not causal of the disease and the reaction is possibly a para-agglutination phenomenon, although this explanation is not universally accepted. With the exception that cross-agglutination of *B. proteus O.X.* 19 occurs with sera derived from cases of louse-typhus and murine typhus, the reaction is specific. (Sera derived from cases of tick or mite typhus agglutinate suspensions of *B. proteus O.X.K.* but not, or only slightly, suspensions of *B. proteus O.X.* 19.) Agglutination in a dilution of at least 1 in 200 is necessary for diagnostic purposes. The titre rises, and near the end of the attack may exceed 1 in 600.

Treatment.—The treatment of typhus until very recently (*vide infra*) has been symptomatic and directed to posture, care of the skin to avoid pressure sores, strict oral hygiene, control of the nervous manifestations and maintenance of the heart's action. Some of the older clinicians insisted upon an abundant or superabundant supply of alcohol and regarded it as the sheet anchor. These large doses of alcohol are unnecessary in typhus ; as in enteric fever, however, the judicious exhibition of stimulants to tide the patient over a critical phase has undoubtedly saved life.

Giunta and d'Ignazio (1939), on the analogy of other severe infective conditions and as the result of their experience of typhus in Abyssinia, suggest that the hæmorrhagic lesions may be due to C-hypovitaminosis, and that B-hypovitaminosis may be the cause of the vascular and neural lesions.

They have adopted the following treatment : (i) intravenous injection of 2 c.c. of 1 per cent. mercurochrome daily for five or six days ; (ii) intravenous injections of 25 cgm. of ascorbic acid, twice to four times daily ; (iii) intramuscular injection of 10 mg. of vitamin B_1 (Betaxin) twice daily ; (iv) lumbar puncture if the cerebrospinal fluid is under pressure ; and (v) symptomatic treatment with subcutaneous glucose and ordinary cardiac stimulants. They claim favourable results.

Convalescent serum has also been employed.

Prophylaxis.—1. *General Measures.*—Systematic lousing is the essential prophylactic measure applicable upon a large scale. The description of methods of disinfestation is outside the scope of a clinical textbook (*vide* footnote, p. 405).

2. *Personal Precautions.*—The precautions to be taken on the admission to hospital of a patient even *suspected* to be suffering from typhus *are of the utmost importance to observe if spread of infection to the staff is to be prevented.* Medical and nursing staffs detailed for duty in typhus receiving rooms or wards *must* wear protective clothing to avoid infestation by lice derived from the patient. The most suitable garment for men or women is a boiler-suit with the legs continued into "feet." The wrists must be tightly buttoned. Gum-boots and rubber gloves coming well over the wrists must be worn. Men's hair must be covered by a cap ; women's hair must be kept short and be covered by a coif. Masking is also desirable. Accommodation should be provided similar to that in smallpox hospitals, where the staff can change into protective clothing and, after duty, take it off in a separate room, leave it for disinfection, pass to a bathroom and finally to the room where

their ordinary uniform hangs. The patient himself must be taken to a special bathroom, stripped, his hair cut, loused, bathed in a bath containing a disinfesting solution and clad in hospital garments by protected attendants before being admitted to the ward—if feasible, a one or two bedded chamber. The patient's own clothing is either disinfested or destroyed.

3. *Specific Vaccine Prophylaxis.*—Rickettsia vaccines have been used with success for large-scale prophylaxis. Weigl's vaccine consists of *killed* Rickettsiæ and is prepared by injecting lice through the anal aperture with *R. prowazeki* and allowing the organisms to multiply for a week, the lice meanwhile being fed upon immune subjects. The lice are then ground up in phenolised saline. The drawback to the method is the number of lice required; from 90 to 100 " prepared " lice are required to afford the three doses of vaccine necessary for the protection of one person. The perfection of methods of tissue-culture will doubtless result in the propagation of virus for vaccines without resort to the louse as a propagator. Blanc employs a *living* vaccine prepared from *R. muricola.* (There is cross-immunity between louse and murine typhus, which, however, is a milder disease.)

On the question as to whether killed or living vaccines should be employed in mass-prophylaxis the *Bulletin of the Health Organisation of the League of Nations* (1938, p. 357) may be quoted: " Living vaccines confer longer and greater protection than killed vaccines and should be used in the presence of an epidemic. In a country free from the disease it is wiser to avoid the introduction of living virus, and killed vaccines should therefore be used if prophylaxis is considered necessary. Standard methods of lousing should be organised and carried out vigorously." To check an epidemic with Weigl's vaccine it is enough to vaccinate 30 per cent. of the population (Radlo, 1938). For the protection of contacts *convalescent serum* has been employed.

II. Trench Fever

(" *Five Day Fever* ")

Definition.—Trench fever is caused by *Rickettsia quintana* conveyed by the louse. It appeared among troops during the war of 1914-18 and disappeared at its end. The disease is characterised by an abrupt fibrile onset, severe shin pains, bouts of shivering and sweating and a rose macular rash. One

or more relapses occur. Great debility and mental depression may result.

Ætiology.—Large numbers of obscure pyrexial attacks with relapses occurred among the troops in France and on other fronts during the war of 1914-18. The ætiology of the condition labelled "trench fever" was investigated by both British and American Commissions. After the Armistice and the dispersal of troops the disease disappeared, although it is reported (Werner, 1939) that from time to time the disease still occurs in Poland, Galicia and Japan. Largely as the result of the work of Arkwright and Bacot (1919) and Ledingham (1920), it was established that the disease was louse-borne and that Rickettsiæ were constantly to be found in the excrement of lice derived from trench-fever patients.

Causal Agent.—It is generally accepted that *Rickettsia quintana*, one of the *extracellular* Rickettsiæ, is the causal agent.

Transmission.—This is the same as in typhus (*vide supra*), viz., autoinoculation, by scratching, of louse excrement deposited upon the skin, but the British Trench Fever Commission insisted upon the infectivity for prolonged periods of dried louse excrement, thus anticipating by many years the recent conclusion as to this source of infection in typhus (*vide supra*).

The patient suffering from trench fever is, *after* the first three days of the attack, infective for lice during the whole of the illness and for a considerable period afterwards. The causal organism may also be excreted in the sputum and the urine. The *infected* louse, which it appears suffers no ill-effects, being purely a vector, becomes *infective* for another host after a latent period of a week or so. During this period Rickettsiæ have multiplied in the lumen of the gut and are then passed in the excrement.

Morbidity and Mortality.—Trench fever caused much and prolonged ill-health, but was rarely fatal.

Blood Picture.—There is usually leucocytosis with polymorphocytosis (80 to 90 per cent.) during the pyrexial periods. The white cells increase at the time of a relapse. Leucopenia sometimes occurs.

Incubation Period.—The incubation period may range from **fourteen to thirty days.** It is stated that shorter periods may obtain following heavy infections.

Clinical Features.—The British Commission on Trench Fever pointed out that *true* trench fever is a *relapsing* fever, but that it was apt to be confused with "pyrexia of unknown

origin" (P.U.O.) of "influenzal" or "enteric" type with similar clinical features.

The War Office Investigation Committee (see "Memoranda on Medical Diseases in Tropical and Sub-tropical Areas" (1919), p. 249) recognised two forms of pyrexia occurring at *different stages* of the disease with the following sequence :—

1. Irregular remittent or intermittent fever for a period rarely exceeding four weeks.
2. Definitely intermittent fever often showing a regular periodicity and sometimes extending over a period of many weeks.

"These two together constitute the complete pyrexial wave of the disease. The *first form presents three types of temperature curve* :—

> "(*a*) A short influenza-like fever wave, lasting about three days; (*b*) a similar wave followed, usually on the 6th, 7th or 8th days, by a febrile relapse, the interval being afebrile; and (*c*) the initial wave may run, more or less, into the relapse and produce . . . a pseudo-typhoid temperature."

"The *second* form of fever only occurs *late in the disease*; it may follow immediately on the first form, or may not appear for many months, the disease in the meantime being apparently in quiescence."

The *onset* is sudden and is characterised by severe headache and pain behind the eyes, particularly when they are moved. Extreme lateral movement of the globes may elicit nystagmus. In addition to headache the patient complains of giddiness and of severe pains in the back and limbs, particularly in the *shins*. The conjunctivæ are injected but the expression of the eyes is bright. There are no marked catarrhal symptoms. The temperature rises abruptly to 103° to 104° F. The pulse-rate is increased proportionately but during convalescence may become unduly slow, although tachycardia is readily produced by exertion. The tongue is dry, the dorsum being covered in the centre by yellow fur. Herpes labialis frequently occurs. The spleen is usually palpable. The bowels are constipated. Albuminuria is common.

A *rash* appears in most cases, sometimes at the onset, sometimes two or three days later, or its appearance may be delayed until a relapse occurs (R. P. Strong). It consists of a few up to one or two hundred rose spots which appear upon the chest, back and abdomen. The spots are not palpable; they

disappear on pressure and may fade in twenty-four hours or so. A papular rash is also described.

The most distressing features of the illness are the pains in the limbs, particularly in the shins, which may become so tender that the patient cannot endure the weight of the bed-clothes. The pains, which may be aching or shooting, tend to shift about from one limb to another and to become worse in the early evening; they may make sleep impossible, and the patient becomes debilitated and depressed, particularly, of course, if several relapses occur. Another characteristic feature is the occurrence of bouts of shivering and sweating. The initial attack may last for three days or so, the illness subsequently taking one of the forms detailed above.

Sequelæ.—Debility, anæmia and mental depression are produced by the prolonged illness, and myocardial degeneration results in tachycardia and dyspnœa on exertion—the so-called "irritable heart." Tenderness over the shins may persist for months.

Diagnosis.—It may be impossible to diagnose trench fever except by exclusion, or until the form of the temperature chart makes the nature of the illness evident. The combination of sudden pyrexia, headache, pains in the back and limbs, conjunctival injection, a pink macular rash appearing within a few days of onset and slight splenomegaly, is common in the early stages of several diseases. The shin pains, the bouts of shivering and sweating and the relapses are highly suggestive.

Among the diseases likely to be confused are mosquito-dengue (particularly), sandfly-dengue, influenza (*q.v.*), undulant fever (*q.v.*), relapsing fever (*q.v.*), the milder types of Weil's disease (*q.v.*), and typhus (*q.v.*) and possibly paratyphoid (*q.v.*). Some of the conditions, *e.g.*, the dengues, may be excluded on geographical grounds, but the accessory aids to diagnosis noted under typhus (*supra*) should always be employed.

Treatment.—This is purely symptomatic and is directed to the alleviation of the bone pains by analgesics and local applications to the shins, and to the management of convalescence which must be prolonged because of the myocardial weakness.

For very severe pains, unrelieved by such drugs as aspirin or phenacetin, vinum colchici has been recommended, or, if this fails, lumbar puncture.

Prophylaxis.—The general measures of disinfestation and the personal precautions on the part of attendants are the same as those for typhus (*vide supra*).

III. Epidemic Relapsing Fever

(*European or Louse-relapsing Fever*)

Definition.—Epidemic relapsing fever is caused by *Spirochæta recurrentis* conveyed by the louse. The onset is quite sudden; a rigor, pyrexia or hyperpyrexia, severe frontal headache and giddiness, vomiting, pains in the back and limbs, particularly in the muscles of the calf, are common. Prostration is early and severe. Fleeting rose spots may appear. The initial attack lasts for four or five days and terminates by crisis. One or more relapses occur, each separated by about a week of apyrexia.

Ætiology.—Epidemic or European relapsing fever, known in the past by various synonyms, *e.g.*, famine fever, is one of a group of relapsing fevers caused by spirochætes. It is conveyed by *Pediculus humanus* (chiefly *P. corporis* but also *P. capitis*), whereas the other members of the group are conveyed by various ticks and are endemic (see Buxton *op. cit.*). Epidemic relapsing fever occurs under the same conditions of want and overcrowding as typhus, and epidemics of both diseases are frequently concurrent. Like typhus, relapsing fever was at one time prevalent in this country, and is one of the "continued fevers" described by Murchison, but is now extinct. Endemic centres still exist in Eastern Europe, North Africa, India and Persia, and China. Like typhus, and for the same causes—propinquity and prevalence of lousiness—the disease is more prevalent in cold weather. All *ages* may be affected, although the disease mainly affects adults; but age and *sex* incidence are determined by the type of community at risk.

Mortality.—This varies greatly, but in some epidemics has been estimated to attain 25 per cent. Case-fatality rates depend largely upon the prompt institution of specific treatment, and also upon the incidence of concurrent infections, such as typhus, malaria and plague.

Causal Agent.—The causal agent is the *Spirochæta* (*Borrelia*) *recurrentis* of Obermeier. It is a spiral filament from 10 to 20 μ long and about 0·3 μ broad, with from five to seven regular coils 2 to 3 μ long by 1 μ in amplitude (Mackie and McCartney). The organism is Gram-negative but stains well with Leishman's stain. During the febrile stage of the primary attack, or a relapse, it can be detected in suitably stained blood smears. It may be abundant or seen only after prolonged search, especially if the blood is obtained during a relapse. Blood taken during the afebrile intervals yields negative results, although

the spirochætes are then present in the spleen. Some are there destroyed by the large mononuclears, but some reappear in the peripheral circulation at the time of a relapse.

Transmission.—For a day after they have sucked the blood of a patient in the febrile phase of relapsing fever, spirochætes can be found in the gut of the louse. Many are destroyed, but some, although they cannot as a rule be demonstrated alive in the gut or in the body of the insect, persist either as spirochætes or in some other form.

P. A. Buxton (*op. cit.*, p. 71) says that "from the sixth day (at 82° F.) spirochætes begin to appear in the blood of the insect which circulates through its body cavity (hæmocœl.). They increase rapidly and may be found in all parts of its body and limbs, but they cannot be found inside the lumen of any part of the gut or inside the salivary glands or ducts. . . . They persist throughout the insect's life. . . . When the spirochæte has reached the body cavity of the louse it has no natural means of egress . . . for it can neither be transmitted by the bite nor voided in the excrement. . . . Transmission normally occurs by the man rupturing a louse and inoculating himself by scratching."

Pathology.—At autopsy cutaneous ecchymoses may be noted. The spleen is considerably enlarged and soft, and occasionally found to be ruptured. The mesenteric lymphatic glands are enlarged. Myocardial degeneration is usually evident and signs of bronchitis, bronchopneumonia or lobar pneumonia are not uncommon.

Blood Picture.—Apart from the presence of spirochætes, there is leucocytosis. The red cells are diminished in numbers and in hæmoglobin content (*cf.* typhus).

Incubation Period.—The incubation period ranges from **five to ten or eleven days,** but periods varying from a few hours up to two weeks have been recorded.

Clinical Features.—An attack of relapsing fever consists in (i) an acute febrile phase terminating by crisis after a period of four or five days (sometimes protracted to eight or even ten days), (ii) an afebrile phase of about a week follows, and then (iii) a relapse occurs, generally, but not always, less severe than the primary attack. Although in European relapsing fever one relapse is more usual, second and third relapses separated by afebrile phases may occur. These later relapses may be represented by a single "spike" of temperature, and spirochætes may not be found in smears of the blood.

It is important to appreciate the clear-cut character of the febrile attacks, separated one from the other by periods of

complete apyrexia. (The failure of the temperature to fall after a few days in an indubitable attack of relapsing fever, or in a few hours after the injection of neoarsphenamine, should suggest a concurrent infection, especially typhus or malignant tertian malaria.)

The *onset* is *quite* sudden, the attack commencing with chilliness, a rigor or convulsion, or sometimes a meningeal reaction. The temperature rises abruptly to 104° or 105° F., and the pulse becomes correspondingly rapid ; it may attain a rate of 120. The patient complains of severe frontal headache and giddiness, and of pain in the back and limbs ; in the muscles of the calf these may be so severe as to prevent walking. Vomiting commonly occurs. The tongue is furred but moist, and usually remains so throughout the attack. Anorexia and constipation but great thirst are usual, so, too, are oliguria and albuminuria. Epistaxis, hæmatemesis, hæmoptysis and hæmaturia may occur. In about a third of the cases mild jaundice is a feature. The liver is moderately, the spleen considerably, enlarged. General lymphadenitis has been recorded.

In some cases an eruption of rose spots appears upon the trunk ; the spots soon fade. In more severe attacks cutaneous petechiæ may appear. Hæmorrhagic attacks with bleeding into the skin and from mucous membranes have been encountered.

Prostration soon becomes severe and in a few hours violent delirium may develop. This condition continues with increasing prostration for from four to five days on the average. The patient may die during the attack of myocardial failure or from bronchopneumonia or lobar pueumonia. Unfavourable signs are diarrhœa, meteorism and hiccough. Usually, however, he awakes after a critical fall of temperature a different being—only to become a sick man again from seven to eight days later on the occurrence of a relapse, unless he has received specific treatment.

Complications.—The chief complications are bronchopneumonia, lobar pneumonia, suppurative parotitis and diarrhœa. Rupture of the spleen has also occurred.

Associated Infections.—The most usual concurrent infections are typhus and malaria (relapse in a malarial subject). Concurrent relapsing fever and bubonic plague have also occurred.

Diagnosis.—The identification of the *Sp. recurrentis* in blood films clinches the diagnosis. Later, when relapses have occurred, the character of the temperature chart is almost unmistakable. Failing the identification of the spirochæte, the prompt therapeutic response to an intravenous injection of neoarsphenamine (*vide infra*) is in itself diagnostic.

Differential Diagnosis.—The following are among the conditions confused with relapsing fever in Mesopotamia during the last war: Typhus, malaria, enteric group infections, cerebrospinal fever, the prodromal stage of smallpox and plague. Weil's disease and trench fever must also be excluded. With the exception of malaria and plague all these diseases are described in this book. Accessory methods of diagnosis (*vide supra* typhus) may be necessary for their exclusion.

Treatment.—The general management of the case is the same as that for typhus. Special care must be taken in the feeding of the patient after a crisis; he may then be ravenous, but large meals must be avoided. Feeds must be given on the principle of "little and often," lest distension and syncope or enteritis result.

Specific Treatment.—A single injection of neoarsphenamine is virtually specific. The dosage may be based upon the body-weight (10 mg. per kilo) or, for adults, a dose of 0·3 to 0·45 gm. may be employed. The drug must be injected during the febrile period, but preferably not at its acme, since collapse may then follow. Albuminuria is not a contraindication. The precautions prescribed for making the solution in freshly distilled water at the correct temperature (68° to 71·6° F.) must be adhered to, the dose being dissolved in 5 c.c. of water. The solution must be injected into the vein slowly, and the greatest care must be taken to prevent the solution entering the tissues around the vein, otherwise troublesome sloughing may result.

A single dose usually suffices; it curtails the attack and prevents relapse, but if relapse does occur, the injection must be repeated.

Prophylaxis.—The general prophylactic measures and the personal precautions are the same as those employed in the control of typhus and trench fever (*vide supra*). Masking is particularly important; infection has been reported from blood accidentally squirted on to the face. The organism has been recovered from the tears and sweat and, like the *leptospira* of Weil's disease (*q.v.*) and *Rickettsia prowazeki*, *Sp. recurrentis* can pass through mucous membranes (*e.g.*, the conjunctiva), but also through the intact skin.

SUMMARY OF CHAPTER XXXIV

Infective Agents.—Epidemic typhus: *Rickettsia prowazeki*. Trench Fever: *Rickettsia quintana*. Epidemic Relapsing Fever: *Spirochœta recurrentis*.

Mode of Transmission.—All are conveyed by *Pediculus humanus.*

Symptoms.—Onset abrupt or sudden in R.F.; headache, pains in limbs (shins, T.F.; calf muscles, R.F.). *Rashes:* on trunk and limbs in typhus; on trunk in T.F. and R.F. Rash lingering in typhus (late petechial elements); fleeting rose spots in T.F. and R.F. Petechial rash sometimes in R.F. *Pyrexia* sustained for two weeks in *typhus* and *no* relapse; variable in *trench fever*, relapses being either clear-cut or merging; the illness may last for weeks. In *relapsing fever*, relapses are clear-cut and alternate with apyrexial periods.

Treatment.—*Typhus and Trench Fever:* Symptomatic. *Relapsing Fever:* Neoarsphenamine is specific.

Prophylaxis.—General: systematic lousing for all three. Specific vaccines for typhus. Personal precautions for attendants identical: boiler suits, gum-boots, rubber gloves, caps and masks.

CHAPTER XXXV

EPIDEMIC INFLUENZA

DEFINITION.—Influenza is a highly infectious, acute febrile illness caused by a filterable virus. Although endemic, it may assume widespread epidemic or pandemic proportions. A specific clinical picture has not yet been defined, but constitutional disturbance and respiratory manifestations are customary. Nervous and gastro-intestinal symptoms, formerly considered ordinary manifestations of the disease, are now regarded by some observers as not truly influenzal.

Ætiological Agent.—Recent views on the cause of influenza are derived chiefly from the work of Laidlaw, Andrewes and their co-workers at the National Institute for Medical Research. Smith, Andrewes and Laidlaw (1933), searching for a laboratory animal susceptible to the suspected virus, discovered that filtered nasal washings from patients with epidemic influenza, when instilled *intranasally* into *ferrets*, produced an influenzal syndrome transmissible to other ferrets. Confirmation that the virus was responsible was forthcoming when one of the Institute's team, accidentally infected from a sneezing ferret, was subsequently found to have developed antibodies to the virus in his blood serum, which previously had been negative. It is now known that as many as thirty-nine or more strains of the virus exist, but the antigenic differences are not so clearly defined that the strains can be separated into types like diphtheria bacilli. The virus exhibits biological instability, and Andrewes (1938) suggests that mutations are first associated with alterations in antigenic structures, with consequent changes in pathogenicity for laboratory animals and for certain tissues. Thus by passage the ferret-pathogenic virus becomes pathogenic for mice (now used as laboratory animals) ; and a lung-adapted strain of the virus is more likely to cause serious pulmonary complications. The virus can be recovered from garglings and nasal washings of patients with true influenza and can now be grown on developing chicks.

Before the discovery of the virus the *H. influenzæ* recovered by Pfeiffer (1892) from a large number of cases in the epidemic of

that year was long regarded as the probable ætiological agent. It can be found in a large number of normal people and is not invariably present in the disease. In the pandemic of 1918-19 the organism was absent in the summer wave of 1918 but present in the wave of 1919. Like the *hæmolytic streptococcus*, it is a secondary invader, liable to appear in certain outbreaks only. The combination of these organisms with the virus, particularly a lung-adapted strain, is to be regarded as increasing the liability to serious pulmonary complications. Some support for this view is available from experimental work on pigs. Swine influenza due to a virus similar but serologically different from the human virus is a mild disease; if, however, the virus is associated with *H. influenzæ-suis*—similar to the human bacillus—serious pulmonary effects result.

Whilst the virus is recognised as the cause of *epidemic* influenza, such as occurred in 1936-37, it has not been isolated from certain local epidemics and from many sporadic cases clinically similar. This must be attributed in part to the various clinical conditions included under "influenza," but it is "possible that there is another virus which causes epidemics of an influenza-like disease in man" (Andrewes, 1938).

Stuart-Harris, Andrewes and Wilson-Smith (1938), investigating two somewhat similar outbreaks of acute respiratory catarrh at the Royal Naval Hospital, Chatham, during November 1936 and January 1937, failed to isolate the virus in the earlier, which they therefore labelled "febrile catarrh," but succeeded in the later, which they diagnosed as true influenza. It is not known if the pandemic of 1918-19 was due to the virus now regarded as responsible for influenza. From serological evidence Laidlaw (1935) suggested that the pandemic strain was transmitted to pigs and survives as the virus of swine influenza, the present human strain being new. This has not been proved and the serological evidence is capable of other interpretations.

Immunity.—Both *virus-neutralising* and *complement-fixing* antibodies appear in the blood serum of convalescents, the former being the subject of much investigation. Variations in the capacity of sera to neutralise different strains of the virus emphasise the antigenic differences in the strains and one of the difficulties of acquiring immunity to the disease (*vide* Prophylaxis *infra*). Neutralising antibodies to both swine and human viruses are present in the sera of a high percentage of normal people; and during epidemics many who remain perfectly healthy exhibit a substantial rise in these antibodies, thus establishing the existence of *latent* infections.

The immunity conferred by an attack of the disease cannot be accurately gauged, but is usually regarded as of short duration for repeated attacks are common. This may in part be due to difficulty in deciding if subsequent attacks are truly influenzal, in part to the variations in strain ; but recent work (Andrewes, 1939) suggests a further explanation. A solid immunity, *i.e.*, an immunity high enough to protect against the disease, is common in virus diseases, and an explanation offered is that the virus, *persisting* in some reservoir of the body after clinical recovery, maintains a stimulus to the immunity mechanism : this *infection-immunity* is regarded as absent in influenza.

Prophylaxis.—*Active Immunisation.*—Experimental influenza in ferrets can be produced with certainty only when the virus is introduced intranasally ; subcutaneous injection does not usually result in disease, but stimulates immunity. The degree is not so great as that resulting from a natural attack of the disease (Grade A immunity of Andrewes), but it does protect against contact infection ; even the nasal instillation of a highly lung-adapted virus, whilst it may result in influenza, does not cause pneumonia (Grade B immunity) ; moreover, a waning Grade A immunity is stimulated to return to its original level by such vaccination with a *living* virus. Dead virus is not so efficient.

In man, attempts at vaccination with a *formolised* virus are encouraging, but serological differences in the virus have caused difficulties in producing a suitable antigen capable of stimulating immunity to all strains. A *living*, passage strain of virus has also been tried and reported upon favourably. Andrewes (1938) estimates that the time to inoculate is a month or two before the expected epidemic. The work is still in the experimental stage.

Passive Immunisation.—There is evidence that prevention or attenuation of attacks can be produced by convalescent serum.

Epidemiology.—Influenza is a disease of antiquity and its most striking epidemiological features are the extreme rapidity with which it spreads and the widespread epidemics or pandemics which occur from time to time. It is also regarded as endemic with a seasonal prevalence in the winter months, but " in years in which there is no major epidemic, the minor outbreaks labelled influenza usually fail to yield a ferret-pathogenic virus. On the other hand, at epidemic times, as in early 1933 and 1937, it has been easy to recover the virus from the large majority of garglings tested " (Andrewes, 1938).

Pandemics occurred in 1847-48, 1889-92 and 1918-19. The "Spanish flu" of 1918-19—so-called because, spreading to Europe from the East, it affected Spain early—was the most widespread pandemic in history and was "one of the great pestilences of mankind, destroying more lives in a few months than did the Great War in four years" (Topley and Wilson, 1936). Different outbreaks of influenza exhibit extreme variability in age incidence, predominant clinical manifestations, association with pneumonia, case-fatality rates and age-groups with the highest mortality. This diversity is also seen in particular outbreaks. The pandemic of 1918-19 exhibited three waves. In the *first* wave (May 1918) gastro-intestinal and nervous manifestations predominated, and in Great Britain naval and military forces in ports and coastal towns were first affected. The *second* wave (Autumn 1918) was the most fatal: deaths were due chiefly to a fulminating pneumonia, and a relatively high percentage of them occurred in children two to five years of age. In the *third* wave (early 1919) deaths were also due to pneumonia, but the case-fatality rate was only one-third of that in the second wave.

Epidemics in Great Britain have in recent times appeared at four-yearly intervals and the case-fatality rates have been much lower than in the great pandemic. The last epidemic, in the early part of 1937, was essentially a respiratory disorder. Deaths from pneumonia occurred chiefly among old people and children.

In *inter-epidemic periods* the disease exhibits a winter incidence, but doubt has been cast on the diagnosis of some of these outbreaks because of the difficulty in recovering a ferret-pathogenic virus (*vide supra*).

The variations in influenza have been attributed to several factors: to enhancement or mitigation in the virulence of the virus; to differences in the predominant strain of the virus and of its associated secondary invaders; and to alterations in herd resistance such as was attributed to the Great War immediately preceding the pandemic of 1918-19.

The widespread susceptibility to influenza, its short incubation period and the existence of missed and abortive cases results in such extreme rapidity of spread that the disease appears almost simultaneously in many places and it is often impossible to trace paths of infection. Evidence of spread, however, can be obtained from the peak mortality which, in 1937, appeared in London a week before towns in the south-east of England and two weeks before towns in the north.

The **incubation period** is from **one to three** days.

Clinical Features.—The clinical criteria lack precision and vary in type and severity in different outbreaks. This indefinitiveness, due in part to failure to differentiate other febrile conditions, will remain until clinical syndromes are correlated with the presence or absence of the virus and of neutralising antibodies in the blood stream.

Stuart-Harris, Andrewes and Smith (1938), investigating outbreaks along these lines, attempted to describe a specific clinical syndrome. They removed from the scrap-heap "influenza" cases in which they recovered the virus and found a five-fold or more increase in antibodies. These cases, characterised by constitutional disturbance and a rather dry respiratory catarrh, they called "influenza." The rest of the scrap-heap they renamed "febrile catarrh." Later, however (Stuart-Harris, Smith and Andrewes, 1940), they were unable to distinguish clinically or epidemiologically between these two groups. They therefore called those cases with laboratory evidence of the virus "epidemic influenza" and used the term "influenza" in a clinically descriptive sense. In view of the variability of clinical features in different epidemics it would be unwise at present to exclude from "influenza" syndromes referable to other systems, *e.g.*, nervous and alimentary, which have been recorded in previous epidemics.

In epidemics predominant symptoms may be general, respiratory, nervous or gastro-intestinal, although in any particular outbreak, or in any individual case, combinations may occur. Sometimes involvement of a system, *e.g.*, the nervous system, appears as a complication rather than as part of the original illness.

A. CONSTITUTIONAL SYMPTOMS are almost constant and may be the only manifestation. The onset is usually sudden with two or more of the following: headache, shivering, malaise, anorexia, dizziness, muscular aches and pains, particularly in the back, and prostration of variable degree. Sweating most commonly occurs with the fall in temperature. Sometimes the onset is more insidious with premonitory symptoms referable to the respiratory tract.

B. RESPIRATORY SYMPTOMS are a common accompaniment to the general disturbance, and may, indeed, precede it. Involvement of the respiratory tract varies from a mild upper respiratory catarrh to a fatal broncho-pneumonia. Coryza, cough and sore throat are common and may appear at the onset, but cough and expectoration more constantly develop toward the end of the pyrexial period. Hoarseness is a feature of some outbreaks and substernal soreness, indicative of

tracheitis, sometimes occurs. Dyspnœa is evidence of serious complications. It is convenient to classify the respiratory type of influenza into those resembling febrile catarrh (common cold), those with tonsillitis or pharyngitis, those with bronchitis, and those with broncho-pneumonia.

C. GASTRO-INTESTINAL SYMPTOMS such as anorexia, nausea, vomiting and constipation are not uncommon and are more properly considered as manifestations of the general disturbance. Gastro-intestinal forms of influenza are, however, described, particularly in some outbreaks. General symptoms, abdominal pain, diarrhœa and little or no respiratory symptoms are the chief features. This form is now suspect, as there is little doubt that the recorded cases included many undiagnosed enteral infections. Further work on the correlation of this form with the presence or absence of the virus is necessary to elucidate the position.

D. NERVOUS SYMPTOMS can also be divided into those which are part of the general disturbance and those which are more specifically nervous, some of which are possibly non-influenzal. It is interesting to recall that whole outbreaks of epidemic diseases of the nervous system (*q.v.*) have been diagnosed influenza. In the acute stage headache is sometimes associated with pain behind, and on movement of, the eyeballs. Dizziness has been mentioned above. Restlessness, insomnia and, less commonly, delirium occur. Apart from general muscular pains, sometimes extremely severe, neuralgia or neuritis occurs, but more commonly as a sequel. Mental disturbances from mild anxiety states to psychoses are attributed to influenza. A common after-effect of the attack is a state of depression or actual melancholia, sometimes with suicidal tendencies, which may persist for weeks or months. Encephalomyelitis is recorded, and must be regarded as a possibility in any virus disease, but the difficulty in deciding its influenzal nature will be obvious.

E. SYMPTOMS REFERABLE TO OTHER SYSTEMS are usually those due to complications (*vide infra*).

Physical Signs.—It is characteristic of influenza that *specific* physical signs are conspicuous by their absence. The diagnosis usually depends upon the symptom-complex described above and the existence of *pyrexia*. Even in the presence of catarrhal symptoms referable, for example, to the respiratory tract, local physical signs are commonly absent or inconspicuous ; thus sore throat may be a prominent symptom, yet the fauces may be merely injected ; cough may be troublesome, yet nothing found on examination of the chest. This absence of physical

signs is a useful diagnostic point, but it has two serious disadvantages: (i) it is not constant, (ii) it is responsible for the inclusion under "influenza" of many non-influenzal conditions in which physical signs are absent or have been missed.

Pyrexia is the most constant sign. In simple influenza it is usually sudden in onset, moderate in degree (101° to 103° F.); it lasts about four days and settles quickly. Pyrexia is commonly continued, but may be remittent or even intermittent. Variability in all these features of the temperature chart is, however, common.

Stuart-Harris, Andrewes and Smith (1938) report that 23 per cent. of cases examined by them in the 1937 epidemic exhibited the saddle-back curve of Dudley, *i.e.*, two dominant peaks with a lower or normal temperature between, which resembles the "diphasic" chart obtained in experimentally infected ferrets.

Other signs are inconstant. The face is usually flushed and the tongue furred. The pulse is raised in accordance with the temperature, although in 30 per cent. of cases there is relative bradycardia and in 10 per cent. relative tachycardia (Stuart-Harris, Andrewes and Smith). There may be signs of coryza—a little suffusion of the eyes and reddening of the nares; the fauces, usually injected and clean, may occasionally exhibit follicular exudate on the tonsils; bronchitis of the large or smaller tubes may be associated with râles in the chest.

Complications are commonly associated with the presence of secondary organisms such as *H. influenza* and hæmolytic streptococci. *Broncho-pneumonia* is the most serious complication and is responsible for a high percentage of the deaths. During the pandemic of 1918 a grave type occurred. Cough, expectoration, often considerable in amount and blood-stained, cyanosis of a curious heliotrope shade, little or no clinical evidence of consolidation of the lungs, and a rapidly fatal termination were the features. In most epidemics, however, the type of broncho-pneumonia conforms with the description in Chapter VI. Evidence of serious respiratory trouble usually appears in the pyrexial period of the first few days, but a post-influenzal broncho-pneumonia also occurs. *Bronchitis* has been considered above as part of simple influenza. *Pleurisy* and *empyema* may occur.

Acute otitis media, mastoiditis, sinusitis and their complications are not uncommon, and may be of a severe, even fulminating type (see Chapter VI).

Myocardial weakness out of all proportion to the pyrexia

may be alarming or rapidly fatal. Dilatation, tachycardia, bradycardia or irregularities are not uncommon in convalescence or as sequelæ.

Mental disorders are mentioned above.

Relapses are common and the predominant manifestation may be in some part of the respiratory tract different from that affected in the original attack.

Complications in almost every part of the body are recorded as occurring in influenza, *e.g.*, phlebitis, pericarditis, arthritis, myositis, orchitis, etc. Their influenzal nature is not yet definitely established.

Blood Picture.—Leucopenia in uncomplicated influenza and leucocytosis in convalescence are widely quoted as typical. The leucocytic response has also been used as a prognostic sign. Stuart-Harris, Andrewes and Smith (1938) were unable to confirm that leucopenia was a regular feature of the disease.

Laboratory Aids to Diagnosis.—Examinations for the virus and for neutralising antibodies in the blood serum are at present too expensive in ferrets and too technical for routine use.

Differential Diagnosis.—Although cases of influenza may be wrongly diagnosed at the beginning of an outbreak, once the disease is known to be prevalent true influenza presents little difficulty and errors in diagnosis are commonly "one way," *i.e.*, many non-influenzal conditions are diagnosed influenza. Because of the variability in clinical manifestations, the absence of specific signs and simple confirmatory tests, a vast number of diseases enter into the differential diagnosis. They cannot be considered individually but are here grouped together :—

1. RESPIRATORY DISEASES clinically resembling influenza and distinguishable only by expensive laboratory tests (*vide supra*), *e.g.*, febrile catarrh, acute coryza, tonsillitis, pharyngitis, laryngitis, bronchitis and broncho-pneumonia.

2. PYREXIAS OF UNKNOWN ORIGIN, *i.e.*, conditions with constitutional disturbances and pyrexia in which *specific* or *localising* signs—

(*a*) *have not yet appeared, e.g.*, almost any infectious disease in its early stages ;

(*b*) *are absent, e.g.*, many abortive cases of infectious diseases such as acute poliomyelitis and epidemic encephalitis ;

(*c*) *have not been detected*, either because they are difficult or impossible to elicit on clinical examination, or because they have been overlooked, *e.g.*, lobar pneumonia in which the patch of consolidation cannot be detected ; dysentery, enteric fever brucellosis,

tuberculosis, etc., in which laboratory tests have been omitted or are negative; cerebrospinal fever in which the cerebrospinal fluid has not been examined.

Thus the diagnosis of doubtful cases of influenza depends largely upon the exclusion of other diseases, and this in turn depends in no small measure upon the clinical acumen of the observer and the completeness of his investigations. In consequence "influenza" has been the refuge of the diagnostically destitute, and will remain so until practical laboratory tests have been evolved.

The **period of communicability** is short, for garglings are seldom positive after forty-eight hours from the onset, although "a positive result was obtained as late as the fourth day in one instance of uncomplicated influenza, and even on the sixth day from a patient with influenzal pneumonia" (Stuart-Harris, Andrewes and Smith, 1938).

Treatment.—The nursing measures described in Chapter X and the diet in Chapter XI are applicable. Isolation during the pyrexial period is desirable but not always possible. Other treatment is chiefly symptomatic. Quinine is frequently prescribed, but there is no evidence that its use is well-founded. Aspirin and Dover's Powder (āā gr. v), repeated six-hourly for four to six doses, is a satisfactory routine prescription in the early stages. Cough, sore throat, headache and hyperpyrexia are symptoms most frequently requiring treatment. For secondary coccal infections the sulphonamide group of drugs should be prescribed.

SUMMARY OF CHAPTER XXXV

Causal Agent: Strains of a ferret-pathogenic, filterable virus found in the upper respiratory tract.

Symptoms: Variable: constitutional, respiratory, gastro-intestinal and nervous.

Signs: Non-specific; *pyrexia* the most constant.

Aids to Diagnosis: Recovery of virus from garglings; presence of neutralising antibodies in blood serum: too complicated for routine use.

Prophylaxis: Satisfactory vaccine not yet produced.

Treatment: Symptomatic.

CHAPTER XXXVI

TETANUS

(*Lock Jaw*)

DEFINITION : A frequently fatal toxæmia of the nervous system arising from a local infection with *Clostridium tetani*. The local lesion is usually a wound of the skin contaminated by earth containing the bacillus or its spores. The characteristic clinical feature is a tonic spasm of the voluntary muscles aggravated by distressing paroxysmal contractions, occurring first and principally in the muscles of the jaw and neck (lockjaw) and secondly in the trunk and limbs.

Ætiology.—The disease is of world-wide distribution, affects persons of all ages, and is prevalent wherever land is cultivated. The causal organism is a normal inhabitant of the alimentary canal of many herbivora, *e.g.*, horses and sheep. Their fæces used as manure infect the soil, in which spores persist for long periods, particularly below the surface ; street dust is similarly contaminated. Whilst these animals are the primary source of infection in man, investigations for such a source would be purely academic since the organism is so widespread. Nevertheless certain districts are known to be more heavily infected and " outbreaks " occur.

Tetanus is an *inoculation* disease and *trauma* is an invariable antecedent, although the injury through which the organism enters may be so small as to be overlooked or forgotten, hence *idiopathic tetanus* ; or the nervous manifestations may not appear until the local injury is healed. War is particularly favourable to the occurrence of tetanus ; wounds received in the field are readily contaminated, and the type of wound, the presence of foreign bodies in it, and delay in treatment are favourable to the development of the local lesion from which toxin is absorbed.

Susceptibility is general, but infection is not always followed by disease. The organism may remain quiescent in a healed wound, and operative interference months and even years later may reactivate the organism and initiate an attack of the disease.

Tetanus has followed surgical operations in which imperfectly sterilised catgut (prepared from sheeps' intestine) has been used; formerly it was common in newborn infants, particularly of negroes, the portal of entry being the stump of the umbilical cord (*tetanus neonatorum*); it has appeared after the subcutaneous injection of infected gelatin in the treatment of aneurysm; and a case has been reported in a puerperal woman following the use of a sanitary pad, the infected wool of which was insufficiently sterilised.

Bacteriology and Pathology—*Clostridium tetani*—the tetanus bacillus—is a slender rod which may develop a terminal spore wider than the rod (drum-stick appearance). Two characteristics are particularly important: it is a *strict anaerobe* and its *spores are highly resistant* to heat, antiseptics and other adverse conditions, so that it may remain quiescent but living for years.

The local lesion varies from a superficial scratch to a deep, severely lacerated wound, but local conditions conducive to anaerobic growth of the organism are deep penetration of the tissues, contusion or laceration producing dead tissue, and suppuration due to aerobic pyogenic cocci, *e.g.*, staphylococci. The organism multiplies in the wound and practically never spreads to other parts of the body. The symptoms are due solely to a potent *exotoxin*. Produced locally it is absorbed by the muscles-end plates, travels along *motor nerves* to the central nervous system and there enters into firm combination with nervous tissue, thus causing symptoms. As in diphtheria, the tissue-toxin combination is so firm that it cannot be dissociated or neutralised by antitoxin. If this process is sufficiently widespread, intense or prolonged, a fatal dose of toxin is fixed, and treatment, no matter how intensive, must fail. Some toxin also enters the circulation and thus reaches all tissues. An *antitoxic serum*, prepared from horses, is standardised in *international units* (I.U.) and also in *American units*, the latter being twice the magnitude of the former.

There are no specific post-mortem appearances.

The **incubation period** represents the combined times for the local infection to be established, and for toxin to travel to the nervous system and be fixed there. The speed with which this occurs varies considerably, depending upon the site of the wound, the severity of the infection and the resistance of the patient. The period is commonly **seven to fourteen days** with wider limits of three days to three weeks or even longer. The more protracted periods are usually indicative of milder attacks (*vide* Prognosis) and occur with distal wounds, *e.g.*,

of the feet, with mild infections, and in persons with some degree of artificial immunity.

Clinical Features.—In peace time wounds are most commonly found on the hands and feet, but in war they may occur anywhere. When clinical signs appear, the wound may be in any state from filthy to healed. The essential clinical features are :—

(i) Muscular rigidity due to tonic contraction, at first localised, later spreading more or less rapidly.

(ii) Superimposed paroxysms or spasms which increase in frequency, duration and severity, and are associated with pain which may become agonising.

GENERALISED TETANUS, with a high mortality (50 per cent. or more), starts in the jaw and neck and spreads to the trunk and limbs, although the distal parts of the upper extremities commonly escape.

LOCALISED OR MODIFIED TETANUS, with a very low mortality, starts in the region of the wound and spreads only locally. It was common during the war of 1914-18 in those with some immunity, *e.g.*, those given prophylactic antitoxin late or in inadequate doses.

CEPHALIC TETANUS, a rare, localised form of tetanus following injuries to the head and neck, associated with facial paralysis and dysphagia, is, by contrast, extremely fatal.

In *generalised tetanus* first symptoms are a feeling of tightness of the jaw or slight difficulty in mastication, or slight stiffness of the back of the neck. Occasionally these are preceded by prodromal symptoms such as chilliness or even sore throat. Local premonitory symptoms such as twitching, stiffness and pain in the region of the wound are rare except in the inoculated. With varying rapidity, but generally in a day or two, the rigidity spreads to the trunk and limbs. When fully developed the mouth cannot be opened (*trismus*), hence "lockjaw"; the angles of the mouth are drawn outwards and upwards over the clenched teeth, the forehead is wrinkled and the eyebrows drawn up, resulting in a facial appearance to which the description *risus sardonicus* (sardonic grin) has been applied; the neck and back are stiff and slightly arched (*opisthotonus*); the abdominal wall is rigid; the limbs, except the distal parts, are stiff and usually straight. The superimposed painful spasms may appear spontaneously or be evoked by external stimuli, often of the most trivial kind such as a draught. At first of short duration (a few seconds), spasms become more prolonged (a few minutes), more frequent and agonisingly painful.

Rigidity and spasm may embarrass breathing, talking and swallowing, and rupture of the rectus abdominis may occur during a spasm. The mental faculties are unimpaired except towards the end. Pyrexia is variable ; it is often absent ; terminal hyperpyrexia may appear. Death is due to exhaustion, heart failure, asphyxia or pneumonia, and usually occurs within a week. If recovery occurs, the spasms diminish in frequency and severity and the rigidity slowly passes off.

Aids to diagnosis have little practical application. Isolation of *Cl. tetani* from the wound is difficult because of the presence of other spore-bearing anaerobes. Inoculation of pus into the base of a mouse's tail results in tetanus. Treatment should never wait on the results of these tests.

Differential Diagnosis.—*Trismus,* due to quinsy, septic teeth, etc., is localised to the jaw ; the neck muscles are not involved and the cause can be found if sought. *Muscular rheumatism* or *fibrositis* in the neck produces local stiffness but no trismus. In *strychnine poisoning* there is complete relaxation between spasms, trismus is not early if it occurs at all, and the distal parts of the extremities are involved to a greater degree. In *hydrophobia* spasms are evoked by the sight of water or attempts to drink it ; there is no underlying rigidity and mental disturbance is usual. Rigidity is a feature of *cerebrospinal meningitis*, but spasms and trismus are rare ; the latter is never early, and the cerebrospinal fluid shows typical changes. In *tetany,* involvement of the hands and feet, the typical posture and diagnostic tests differentiate the condition. *Hysteria* and *anxiety states* like tetano-phobia are functional nervous conditions which may superficially resemble tetanus.

Prognosis.—Severe wounds are usually associated with severe attacks, but there are many exceptions. In general the shorter the *incubation period* the worse the prognosis : if it is less than seven days the prognosis is usually bad, if more than fourteen days the prognosis is usually good. The incubation period is, however, an uncertain guide, since it cannot be measured accurately. Cole (1940) places more reliance on the *period of onset of reflex spasms*, which is the interval between the first symptom and the first spasm. This can be gauged more accurately. If it is forty-eight hours or less the prognosis is grave, and *per contra* the longer this period the better the outlook. The sooner *antitoxin* is given after the onset the better the prognosis ; if given in the incubation period it profoundly modifies any attack which appears (*vide supra*). In both cases the antitoxin acts as a prophylactic

(*vide* Prophylaxis and Treatment). Concurrent chronic disease of the heart or lungs, *e.g.*, cardiovascular degeneration, chronic bronchitis and emphysema, render the prognosis much worse. The disease is very fatal in those over sixty years of age and in the newborn. The fatality rates of the various forms of the disease are considered above.

Prophylaxis.—ACTIVE IMMUNISATION, introduced in recent years and now used extensively in armies, follows closely the lines of diphtheria prophylaxis (*vide* Chapter XIII, p. 174). No simple test, like the Schick test, has been evolved for determining susceptibility and the success of immunisation. The antigen used is some form of *tetanus toxoid*, *i.e.*, toxin treated with formalin to destroy the spasm-producing factor but leave the antigenic power. Toxoid-antitoxin floccules and alum-precipitated toxoid have been used, but Boyd (1938) recommends two doses of 1 c.c. of *formol toxoid* spaced at an interval of six weeks. In his series these doses stimulated the production of antitoxin, which appeared in the blood serum to the extent of 0·1 to 0·5 units per c.c.—an amount equivalent to a prophylactic injection of 1,500 units. The antigen is no more likely to cause unpleasant reactions than diphtheria prophylactics, but the subjects are usually older and in them the percentage of reactions is higher than among children (*vide* Chapter XIII, p. 176). The duration of the artificial immunity is at present unknown, but it is suggested that it may decline rapidly, necessitating refresher doses (*injections de rappel*) at intervals, to act as secondary stimuli and maintain the immunity level.

"*Triple*" *immunisations*, using mixed prophylactics against tetanus, enteric fever and diphtheria, have been tried in armies and are apparently successful.

PASSIVE IMMUNISATION by the intramuscular injection of 1,500 units (I.U.) of antitoxin is, in peace time, reserved for those who have received injuries on roads or cultivated lands or in any other circumstances giving rise to the slightest suspicion that infection with tetanus is possible. It should be given as soon as possible after all war wounds, and is particularly important when foreign bodies are embedded in the wound. The immunity conferred cannot be relied upon to last more than fourteen days, so that, in the case of those with protracted, dirty wounds, further injections at intervals of seven to ten days may be desirable. As experience with active immunisation is short, there is still a question of the routine administration of antitoxin in those wounded who have been actively immunised. A prophylactic injection of antitoxin should be given before

surgical operations on old wounds, and the site of such wounds should be avoided for other surgical measures.

Combined active and passive immunisation has also been tried. Antitoxin is given immediately and toxoid later.

GENERAL MEASURES.—Treatment of the wound aims at removing the conditions favourable to the growth of the tetanus bacillus. Foreign bodies must be removed as soon as possible, dead tissue excised, and the wound opened up to secure free drainage and aeration.

Treatment.—Rest in a quiet room with no other patients, the elimination of all possible sources of irritation, and a minimum of examinations and nursing measures are essential to avoid external stimuli which may set up reflex spasms. In view of the exhaustion following spasms, the maintenance of the patient's strength is important. Patients who cannot take food normally should be fed nasally or by a tube inserted between the teeth ; feeds should consist in fluids, glucose, milk and eggs. Rectal feeding is best avoided.

Antitoxin should be administered immediately by the intravenous route in doses of 100,000 to 200,000 units (I.U.) according to the severity of the case. Its action is almost entirely prophylactic, *i.e.*, it prevents any further intoxication of the nervous system. If a lethal dose has been fixed, the outlook is hopeless, but there is no method of determining this, and every case, no matter how late, should be treated. Serum reactions are common, and the advice given in Chapter III, p. 25, should be followed.

Treatment of the *wound* should be deferred for one hour after the injection of the serum. It consists in removal of foreign bodies, excision, drainage and irrigation with oxidising agents such as hydrogen peroxide.

Of symptomatic treatment, the most important is the administration of *sedatives* to relieve rigidity and spasms. Chloral hydrate (gr. xv to xx), potassium bromide (gr. xx four to six hourly) or paraldehyde (ʒ ii) as required (the doses being doubled if given per rectum) may suffice in mild cases. Basal anæsthetics have replaced inhalation anæsthetics in the treatment of spasms. Avertin in full doses is most commonly used and may be given daily or more frequently.

The use of curare to reduce reflex spasms has not proved successful.

SUMMARY OF CHAPTER XXXVI

Causal Agent : *Clostridium tetani*—a spore-bearing anaerobe.

Portal of Entry : Earth-contaminated wounds, penetrating, contused or suppurative rather than clean-cut.

Clinical Manifestation: Rigidity with superimposed painful reflex spasms; first in jaw and neck, spreading to trunk and limbs.

Types of Disease: Generalised; localised or modified.

Prognosis: From incubation period and period of onset of reflex spasms.

Prophylaxis:

Active immunisation with formol toxoid, two doses (1 c.c. each) at six-weekly intervals.

Passive immunisation: 1,500 units of antitoxin repeated if necessary.

Treatment: Antitoxin intravenously (100,000 to 200,000 units); treatment of the wound; sedatives; adequate nutrition; avoidance of external stimuli.

CHAPTER XXXVII

CONTROL OF INFECTIOUS DISEASES IN HOSPITAL

(*For control of infectious diseases in the general population see Chapter IX, p. 73; for prevention of individual diseases see under appropriate chapters.*)

ADMISSIONS to General Wards.—Some diseases, *e.g.*, smallpox, chickenpox and measles, are highly infectious; others, *e.g.*, scarlet fever, diphtheria and whooping-cough, are moderately so; and some, *e.g.*, erysipelas and pulmonary tuberculosis, are of relatively low infectivity. Patients suffering from diseases of high or moderate infectiousness are never treated in general wards, but not infrequently patients with mildly infectious diseases are admitted. The practice is not to be recommended, and, if employed, facilities must be available for the proper barrier nursing of such patients. In general, it is wiser to exclude all patients suspected or known to be suffering from an infectious disease.

Measures which must be adopted on the appearance of an infectious disease in a general ward, or if an intercurrent disease in an infectious ward dealing with a different disease, depend upon a number of factors:—

(i) *The disease and its infectivity*, *e.g.*, the measures necessary on the appearance of a case of smallpox, are much more rigid than for rubella.

(ii) *Whether the patient who developed the disease was incubating it at the time of admission or acquired it in hospital*, *e.g.*, if a patient is infected in hospital with enteric fever, the necessary measures are considerable and involve a thorough search for the source of the infection; but if the disease was incubating on admission a much simpler procedure would suffice.

(iii) *The time which elapsed between the onset of symptoms and the removal of the case.* The longer a patient with an infectious disease has been allowed to

remain in the ward before removal, the more opportunity has there been for the transfer of infection to contacts, and the greater the precautions necessary.

(iv) *The susceptibility of ward contacts, e.g.*, the appearance of a case of measles in a ward of young children will demand much more extensive measures of control than if the disease appeared in a ward of adults.

(v) *The magnitude of the outbreak, e.g.*, different procedures will be necessary on the occurrence of a *single* case of nasal diphtheria and of an *outbreak* involving several patients.

(vi) *Prevalence of an epidemic.*—If among the general population an epidemic is prevalent, *e.g.*, of influenza, cerebrospinal fever or poliomyelitis, more rigid measures are necessary on the occurrence of a single case than if the disease were sporadic.

It will be obvious that no definite instructions can be laid down, even for a single disease. In every instance the various factors should be considered, and if measures adopted fail to control the outbreak more stringent ones should be introduced. In Table XXV the procedures are classified into *compulsory* and *optional*, the latter being subdivided into those which are *usually* carried out, those which are *sometimes* or *occasionally* used, and those which are *rarely necessary*. The compulsory procedures are applicable at *all times* to *all infectious diseases*. Those marked optional are, in certain circumstances, and for certain diseases, compulsory, *e.g.*, nurses should usually be immune to the disease they are treating, but in the case of smallpox, diphtheria, enteric fever and certain other diseases, nurses *must* be immune before being allowed in contact with the disease.

Table XXVI is intended as a guide—an indication of the measures which are usually adequate on the occurrence of a single case. Modifications in the direction of greater or less completeness may be necessary in individual instances. Below, more detailed guidance is given for the control of certain diseases.

CONTROL OF OUTBREAKS OF DIPHTHERIA

No definition of an " outbreak " can be given : sometimes two or more *clinical* cases discovered in a ward, or the appearance of several secondary cases, may be regarded as an outbreak ; at other times it may be desirable to impose a different standard.

TABLE

MEASURES FOR CONTROLLING INFECTIOUS

	Obligatory Procedures
	ALWAYS to be carried out
1. **Disposal of a case** suspected or known to be suffering from an intercurrent infectious disease.	*Barrier nurse immediately* till decision is reached. Then adopt one of the alternative optional procedures.
2. **General administrative actions.**	*Inform parents* or relations, and obtain permission for removal of patient to infectious diseases hospital unless undue delay is caused thereby. *Notify M.O.H.* in the case of notifiable diseases.
3. **Quarantine measures.** May be "complete" or partial. (*a*) *Patients :* Restriction on the *movements* of susceptible contacts.	(No restrictions on known *immune* contacts.) Suspend transfers to other open wards. Suspend transfers to other hospitals, institutions or schools unless the receiving institution has been informed and is prepared to accept the contact.
(*b*) *Patients :* Restrictions on the *admission* of new patients whilst ward is in quarantine.	(Known immunes may be admitted, but see last column.) Patients or their parents to be informed of quarantine and to agree to admission.
(*c*) *Staff.*	...
(*d*) *Restrictions on visitors to contacts.*	Allow patients on the danger list to be visited by near relatives.
	In hospitals for infectious diseases
4. **Search for the source of infection.** *See also* 5.	...
5. **Dealing with contacts :** (*a*) *Examinations :* (i) To determine susceptibles and immunes.	Inquire into previous history of infectious diseases.
(ii) To detect missed cases or carriers.	Clinical examination.
(iii) To detect new cases as they arise.	Regular clinical *observation* during quarantine.
(*b*) *Protection of susceptible contacts.*	...

XXV

DISEASES APPEARING IN HOSPITAL

Optional Procedures * classified according to the frequency with which they are used

USUALLY employed	SOMETIMES employed	OCCASIONALLY employed	RARELY necessary
Remove to an isolation hospital or an isolation unit dealing with the disease.	Isolate in a special chamber cubicle or room.	Retain in the ward on barrier nursing.	...
...	...	...	...
Allow contacts to go home at their own request, but only after they or their parents have been informed and accept responsibility in writing.	Allow contacts to go home at their own request without signing a form of responsibility, but inform them that they are contacts.	Discharge contacts to their own home after informing them or their parents that they are contacts. (Home conditions, the number of other susceptible children in the house and the wishes of the parents should be considered.)	Suspend the discharge of contacts.
In the case of contacts of notifiable diseases, it is desirable to inform the Medical Officer of Health of their movements.			
Suspend the admission of patients not known to be immune. (Mainly for children's wards.)	Suspend admission of children. (Mainly in mixed wards.)	...	(*a*) Suspend *all* admissions. (*b*) No restrictions on admissions.
Nurses treating infectious diseases should be known to be immunes.	...	Prohibit transfer of nurses to other wards.	Exclude students from wards unless known to be immunes.
Exclude children under sixteen years of age.	No restrictions.	...	Suspend visiting days.
visiting is always restricted. The above measures refer to general hospitals.			
Examination of other patients in the ward.	...	Examination of staff as well as patients.	Examination of food and drinks.
...	Immunological examination, *e.g.*, Schick and Dick tests.	...	...
...	Bacteriological and immunological examinations.	...	...
Susceptible children to be kept in bed towards the end of the incubation period of the disease.	...	...	...
...	Passive immunisation.	Active or combined passive and active immunisation.	...

* Optional procedures are *obligatory* in some diseases.

TABLE

INFECTIOUS DISEASES

Measures usually necessary after a single case.

Disease	Disposal of Cases	Quarantine of Susceptible Contacts	Quarantine in Days	Restrictions on Nurses
Smallpox . .	To Smallpox Hospital only after consultation with M.O.H.	Rigid; till released by M.O.H. — *all* contacts.	14	No movements till released by M.O.H.
Chickenpox . .	To Infectious Diseases Hospital.	Under 14—complete. Over 14—partial.	21	No transfers to other children's wards unless immune.
Measles . .	To Infectious Diseases Hospital.	Under 14—complete. Over 14—partial.	14	*Nil.*
Scarlet fever . .	To Infectious Diseases Hospital.	Under 14—partial or complete. Over 14—*nil* or partial.	7	*Nil.*
Diphtheria . .	To Infectious Diseases Hospital.	Under 14—partial or complete. Over 14—*nil* or partial.	7	*Nil.*
Pertussis (whooping-cough).	To Infectious Diseases Hospital.	Under 14—partial. Over 14—*nil.*	14	*Nil.*
Puerperal fever .	To Infectious Diseases Hospital or isolate in hospital.	Partial.	? 14	Nurses must be free from hæmolytic streptococci in nose and throat.
Enteric fevers (typhoid and paratyphoid).	Barrier nurse or otherwise isolate.	*Nil.*	14	Nurses attending case must be immune.
Dysentery . .	To Infectious Diseases Hospital or isolate in hospital.	*Nil* or partial.	14	*Nil.*
Infective enteritis or gastro-enteritis.	Isolate in chamber or barrier nurse.	*Nil* or partial.	? 7	*Nil.*
Mumps . . .	To Infectious Diseases Hospital.	*Nil* or partial.	25	*Nil.*
Rubella . .	To Infectious Diseases Hospital.	*Nil.*	21	*Nil.*
Erysipelas . .	Barrier nurse or otherwise isolate.	*Nil* or partial.	*Nil.*	*Nil.*
Vulvo-vaginitis .	Barrier nurse or otherwise isolate.	*Nil* or partial.	?	*Nil.*
Meningococcal meningitis.	Isolate in chamber or barrier nurse.	*Nil.*	7	*Nil.*
Acute poliomyelitis	Isolate in chamber.	*Nil.*	14	*Nil.*

XXVI

IN GENERAL WARDS

(After the Table in "Guy's Hospital Reports," 1938)

Investigation of Contacts	Treatment of Susceptible Contacts	New Admissions	Visitors to Ward	Remarks
For scars of vaccination.	Vaccination.	Forbidden.	Rigidly excluded.	Immediate *standstill* order of *all* contacts. Immediate consultation with M.O.H.
For scars and previous history of Chicken-pox.	Observation.	Restricted to immune children and adults.	Exclusion of children.	Not dangerous, but very infectious and therefore troublesome.
For previous history of measles.	Passive immunisation.	Restricted to immune children and adults.	Exclusion of children.	Dangerous disease. Err on side of rigidity.
Clinical—for missed cases, carriers, cases of tonsillitis. Occasionally Dick testing and swabbing for hæmolytic streptococci.	Observation. Occasionally passive immunisation.	Restricted to known immune children (Dick-negative) and adults.	Exclusion of children.	State of immunity (Dick test) of all discharged patients should be known.
Clinical — for missed cases, carriers, cases of "tonsillitis," "coryza." Occasionally, Schick testing and swabbing for diphtheria bacillus.	Observation. Occasionally passive immunisation.	Restricted to known immune children (Schick-negative) and adults.	Exclusion of children.	Avoid routine swabbing of contacts. Shick testing should always accompany swabbing. State of immunity (Schick test) of all discharged patients should be known.
For previous history of pertussis.	Observation.	Restricted to known immune children and to adults.	Exclusion of children.	Extend quarantine if any contact develops cough or coryza. Early diagnosis difficult; cough plate the best test.
Nil, unless patient was infected in hospital.	Observation (?sulphonamides).	At the discretion of the surgeon in charge.	No restrictions.	If case was infected in hospital, search for source in all contacts, including staff.
Nil, unless case was infected in hospital.	Observation. Occasionally passive or active immunisation	No restrictions.	No restrictions.	If case was infected in hospital, complete examination of contacts, food and drink and more rigid measures.
Nil, unless case was infected in hospital.	Observation.	No restrictions.	No restrictions.	If case was infected in hospital, search for source and more rigid measures.
Clinical — for missed cases.	Observation.	No infants under two years.	Exclusion of children.	Rigid measures if any suggestion of an outbreak.
Nil.	Observation.	No restrictions.	Exclusion of children.	Not very infectious.
Nil.	Observation.	No restrictions.	Exclusion of children.	Not very infectious.
Nil.	*Nil.*	No restrictions.	No restrictions.	...
Clinical — for missed cases.	Observation.	No restrictions. (Occasionally exclude female children.)	No restrictions.	...
Nil.	Observation.	No restrictions.	No restrictions.	Infectious during first few days only (unless carrier).
Nil.	Observation.	No restrictions.	Exclusion of children.	Infectious during first few days only.

The obligatory procedures laid down in Table XXV must be carried out, especially the immediate removal of definite cases, the isolation and investigation of doubtful cases (*vide* Chapter XIII, p. 158) and the clinical examination of contacts to detect missed cases and carriers. The routine swabbing of all contacts for morphological *C. diphtheriæ* as the *only* measure of control is full of fallacies and is to be deprecated, particularly in a healthy community of contacts such as occurs in schools. It will result in unnecessary restrictive measures, or actual isolation in hospital, of many healthy and harmless persons, such as those carrying diphtheroids or those with transient latent infections.

A. **Full Procedure.**—When extensive investigation is necessary because of the magnitude of the outbreak, the following full procedure for all contacts, patients and staff, should be employed :—

(i) Place the ward in full quarantine.
(ii) Schick test every contact, unless the state of immunity is known.
(iii) Swab the nose, throat and discharges of all contacts.
(iv) Submit any positive morphological swabs for typing or virulence tests. If typing is performed, virulence tests are unnecessary except for *mitis* strains.

In twenty-four hours the result of the swab will be available and in forty-eight hours the result of the Schick test. The results of the tests, the inferences to be drawn and the action to be taken are given in Table XXVII.

B. **Modified Procedures.**—If the outbreak is not serious enough to require the above full procedure, the following modification may be used :—

Examine clinically all patients and staff and divide them into :—

(*a*) *Those with some clinical abnormality of the upper respiratory tract, e.g.*, those with rhinorrhœa, otorrhœa or enlarged tonsils. If among them missed cases are detected, the outbreak is more serious than was at first believed and the full procedure should be adopted. If no missed cases are detected, examine the patients falling into this class as described in the full procedure above. If the source of infection still remains undetected, the full procedure should be employed.
(*b*) *Those without upper respiratory abnormalities.*—Examine daily for seven days after the removal of the source of infection.

TABLE XXVII

Possible Results of Schick Testing and Swabbing Healthy Contacts of Diphtheria; Inferences to be Drawn and Action to be Taken

In Twenty-four Hours		In Forty-eight Hours (and Subsequently).		
Morphological Result of SWAB	Action	Result of SCHICK TEST	Inference	Action
Swab+	Isolate	Schick−	Probably carrier	Await result of typing or virulence test:— (*a*) If gravis, intermedius or virulent mitis types=*true carrier*: send to isolation hospital. (*b*) If non-virulent, withdraw from isolation and treat as "swab negative" case.
		Schick+	Latent infection or Incubating diphtheria	(*a*) If expert supervision is not available, send to isolation hospital. (*b*) If expert supervision is available:— (i) Immunise, either passively with diphtheria antitoxin, 1,000 to 2,000 units; or combine passive and active immunisation, viz., 1,000 to 2,000 units of diphtheria antitoxin and 0·4 c.c. toxoid, followed by two subsequent injections of toxoid (see p. 164). (ii) Re-swab daily; if negative, infection has been overcome and restrictions can be removed; if still positive after one week, treat as carrier. (iii) If at any time clinical signs of diphtheria appear, give antitoxin in therapeutic doses and remove patient to isolation hospital. (iv) If the organism is reported non-virulent, suspend the above measures and treat as a swab negative case.
Swab−	Leave	Schick+	Susceptible but not infected	(i) Keep in quarantine under daily observation. If any clinical signs of disease appear, give antitoxin and confirm by swabbing. (ii) When out of quarantine, actively immunise.
		Schick−	Immune and not infected	No action; no restrictions.

The success of this modified procedure depends largely upon the **efficient watching of contacts.** If secondary cases develop, the full procedure must be carried out. If none occur, no further action is necessary at the end of the quarantine period. Until the source of infection has been detected and eliminated, admission and discharges should be restricted to known immunes; thereafter there should be no restrictions on admissions. If patients are discharged during the seven days' observation, they should be Schick tested and swabbed, and any necessary action carried out before they leave the ward.

C. **Limited Procedure.**—When there are reasonable grounds for believing that a patient who develops diphtheria in hospital was incubating the disease on admission, or where the prospects of transmission to others has been remote, it may suffice to watch contacts for seven days. If subsequent cases occur, more extensive measures may be necessary.

D. **Emergency Measures.**—It occasionally happens that the state of an outbreak and the facilities for dealing with it give rise to anxiety concerning its control by the above procedures. In such circumstances it is justifiable to passively immunise every contact, but the method is to be avoided as far as possible.

CONTROL OF HÆMOLYTIC STREPTOCOCCAL INFECTIONS

A full investigation of the sources and modes of infection of hæmolytic streptococcal outbreaks is frequently difficult and laborious. Two factors contribute considerably to the difficulty :—

(i) The ubiquitousness of hæmolytic streptococci and the incidental frequency of healthy carriers, not all of whom are dangerous or are connected with the outbreak.

(ii) The tendency to underestimate the importance of minor streptococcal conditions capable of initiating outbreaks. Okell and Elliott (1936) showed the frequency with which cross-infection with hæmolytic streptococci takes place in oto-rhinological wards. As far as practicable, cases of acute tonsillitis and septic oto-rhinological conditions should be excluded from general wards. The importance of minor septic conditions in causing puerperal infections was stressed in Chapter XII.

Investigation is rendered much simpler if facilities exist for typing hæmolytic streptococci recovered from cases and

carriers. The method is, however, laborious and technical difficulties may render it impracticable. Nevertheless, whenever possible it should be employed, even in the first case. The knowledge thus gained may be invaluable in subsequent search for the paths of infection.

I. CONTROL OF OUTBREAKS OF SCARLET FEVER

The obligatory procedures laid down in Table XXV must be carried out, especially the immediate removal of definite cases, the isolation and investigation of doubtful cases (*vide* Chapter XII, p. 109) and the clinical examination of contacts to detect not only missed cases of scarlet fever but of tonsillitis and "septic" oto-rhinological conditions. In all outbreaks of scarlet fever a variable percentage of those infected suffer from infectious sore throat because they are Dick-negative: they must be regarded as cases of the disease.

A. **Full Procedure.**—When extensive investigation is necessary because of the magnitude of the outbreak, the following procedure for all contacts—patients and staff—should be employed :—

(i) Place the ward in quarantine.
(ii) Dick-test every contact, unless the state of immunity is known.
(iii) Swab the nose, throat and discharges of all contacts for hæmolytic streptococci.
(iv) Submit positive swabs for typing.
A less satisfactory procedure is to *group* the streptococci (*vide* Chapter XII, p. 91). Those not belonging to Lancefield's Group *A* can be neglected.

If neither typing nor grouping is possible, the profusion of the colonies or their percentage in relation to other organisms on the culture plate provides some evidence of the infectivity of the subject. A low percentage, or a few colonies only, can frequently (but not invariably) be regarded as insignificant, as most dangerous disseminators of hæmolytic streptococcal infections carry large numbers of the organism.

In twenty-four hours the results of the Dick test and swabbing will be available. The results of the tests, the inferences to be drawn and the action to be taken are given in Table XXVIII.

B. **Modified Procedures.**—As scarlet fever is generally mild and its infectivity not very high, outbreaks are seldom serious,

TABLE XXVIII

Possible Results of Dick Testing and Swabbing Healthy Contacts of Scarlet Fever; Inferences to be Drawn and Action to be Taken

In Twenty-four Hours, Results of Tests	Inference	Action
Swab+ ; Dick−	Probably carrier	(*a*) Segregate * and treat, if thought desirable, with sulphonamides. (*b*) Await result of typing of streptococci :— (i) If of same type as the *case*, isolate till bacteriologically free. (ii) If of a different type, but pathogenic, continue segregation if possible, otherwise allow to mix with others.
Swab+ ; Dick+	Latent infection or incubating scarlet fever	(*a*) Segregate.* (*b*) Protect if considered necessary, by :— (i) Concentrated scarlatinal antitoxin (5 to 10 c.c.) or protein-digested scarlatinal antitoxin (0·75 to 1·5 c.c.), or (ii) Administer sulphonamides as for minor ailment (*vide* p. 82). (*c*) Re-swab at short intervals until bacteriologically free. (*d*) If at any time clinical signs appear, remove to hospital as a case of scarlet fever or isolate as a case of infectious sore throat. (*e*) If the organism is reported to be of a different type from that causing the case—suspend the above measures.
Swab− ; Dick+	Susceptible but not infectious	Keep in quarantine under daily observation. If clinical signs of disease appear, treat as scarlet fever and confirm by repeating swab.
Swab− ; Dick−	Immune. Not infected	No action ; no restrictions.

* Isolation of individual cases, the most satisfactory procedure until results of typing are known, is usually impracticable, and segregation is the alternative.

and the full procedure described under *A* is often unnecessary. The following modification may prove sufficient :—

Examine clinically all patients and staff and divide them into :—

(*a*) *Those with some clinical abnormality of the upper respiratory tract, e.g.*, rhinorrhœa, otorrhœa or enlarged tonsils. Carry out the procedure described under *A*, except that passive immunisation with serum may be omitted.

(*b*) *Those without upper respiratory abnormalities*.—Examine daily for seven days after removal of the source. Until the source of infection has been detected and eliminated, admission and discharges should be restricted to known immunes. The state of immunity (Dick test) of patients discharged during the quarantine period should be ascertained.

C. **Limited Procedures.**—Where there are reasonable grounds for believing that the patient who developed scarlet fever in hospital was incubating the disease on admission, or where the prospects of transmission to others have been remote, it may suffice to watch contacts for seven days. This is usually adequate in adult wards.

If the means described under *B* or *C* fail to control the outbreak, the fuller procedure under *A* will be necessary.

II. CONTROL OF OUTBREAKS OF PUERPERAL FEVER

Puerperal fever being a serious disease, it is important to carry out a detailed investigation when cases appear. Attempts should first be made to decide if the patient was incubating the disease on admission or was infected after admission. If the latter, a rigid procedure for the detection and elimination of the source of infection is necessary.

Every case must be treated as of extrinsic origin unless definite evidence to the contrary is available.

(i) *The infected patient* must be removed at once. Bacteriological examination of the genital tract to determine the ætiological agent is essential. Whenever possible hæmolytic streptococci should be typed to assist in tracing paths of infection. A general clinical and, whenever necessary, bacteriological examination to exclude autogenous sources of infection should be carried out.

(ii) *Staff* must receive special attention. The aseptic technique of the ward should be closely overhauled. Clinical examination of staff to detect those with acute or chronic oto-rhinological conditions or septic cutaneous lesions (*vide* Chapter XII, pp. 93 and 126) should be combined with routine bacteriological examination to detect carriers. Here, again, typing of hæmolytic streptococci is desirable, otherwise harmless carriers of organisms unconnected with the outbreak will be excluded from practice and the work of the ward disorganised.

(iii) *Other patients* should be examined clinically and bacteriologically, special attention being directed to discharges and oto-rhinological abnormalities. Rigid quarantine must be imposed for one week after the removal of sources of infection, and terminal disinfection carried out. Other puerperal women who are contacts may be protected by a course of one of the sulphonamide group of drugs (*vide* Chapter X, p. 82).

Current official advice for the control of puerperal sepsis is contained in Memorandum (226 Med.) of the Ministry of Health (1939). Its object is to explain the nature of puerperal sepsis, how it is spread, and how to identify and group the streptococci responsible. Advice is given on the routine examination of midwives and on the measures of control on the occurrence of sepsis. As soon as puerperal *pyrexia* occurs in their practice, attendants must cease to conduct labours or nurse other puerperal women until it is certain that the pyrexia is not due to infection of the genital tract. Bacteriological examination of vaginal swabs from patients and throat swabs from attendants, and *grouping* (Lancefield) of streptococci are recommended. Presumably grouping is advocated in preference to *typing* (Griffith) because of the relatively simpler technique.

CONTROL OF OUTBREAKS OF MEASLES

Measles being a serious and highly infectious disease for which no specific treatment is available, the appearance of a single case demands a rigid procedure for preventing spread :—

1. Passive immunisation of susceptible contacts—*sero-prevention* or *sero-attenuation*—should be used invariably (see Chapter XVI, p. 214). Sero-prevention should be the aim for children in whom an attack of measles would be particularly dangerous, *e.g.*, children seriously ill or under two years of age,

those with respiratory diseases, malnutrition and enteritis, or where for administrative reasons it is impracticable to deal with attacks of modified measles. Two problems commonly arise. Firstly, the classification of contacts into immunes and susceptibles depends upon whether or not the contact has previously suffered from measles ; such histories are frequently erroneous and should, whenever possible, be verified by reference to the medical practitioner or hospital. When in doubt treat the contact as susceptible, as an attack of unmodified measles in a patient erroneously presumed to be immune and not protected may nullify the measures taken to prevent spread. Adults can usually be regarded as immune. Secondly, even when sero-prevention has been the aim, secondary cases commonly occur. All susceptibles are then re-exposed at a time when passive immunity is waning ; a new period of quarantine must be imposed and the disorganisation of the ward protracted. It is therefore desirable, where facilities exist, to quarantine susceptible contacts *separately* in single-bedded chambers. Even when this is impracticable for *all* susceptible contacts, it may be possible for a *selected few*, such as those liable to suffer severely from an attack of measles, even when modified by serum. All contacts should be watched for early signs of measles during the quarantine period, and, if retained in an open ward, should be kept in bed in the second week after exposure.

CONTROL OF OUTBREAKS OF CHICKENPOX, RUBELLA AND MUMPS

These diseases are grouped together because they exhibit common features. They are seldom dangerous but, because of their long incubation period, they cause considerable disorganisation of ward routine. No tests for determining susceptibility or immunity and no certain passive prophylactic agent is known, although seroprophylaxis of susceptible contacts has been tried in chickenpox and mumps (see Chapters XXI and XIX). Fortunately in the case of chickenpox the existence of scars is positive evidence of immunity. In all other cases dependence must be placed upon the history, which may be erroneous.

Cases of the disease must be removed from the ward as they occur. The primary case is usually a patient incubating the disease on admission, or a missed case ; carriers are not known to occur. Contacts must be kept under observation at least daily. In the last week of quarantine children should

be kept in bed so that they can be closely watched and are not in close proximity when secondary cases are beginning to appear. When facilities exist for dividing up a group of contacts—preferably into single-bedded chambers—it is possible to avoid more than one "generation" of secondary cases.

CONTROL OF OUTBREAKS OF WHOOPING-COUGH

A procedure similar to that described for chickenpox, rubella and mumps is usually employed. Because of the difficulty in diagnosing early whooping-cough, every contact who develops coryza or a cough must be isolated immediately. This may be impossible in contacts already suffering from some upper respiratory disease such as measles. Vaccine prophylaxis and convalescent serum for contacts may be tried but is uncertain (*vide* Chapter XV, p. 194).

CONTROL OF OUTBREAKS OF INGESTION DISEASES

(Enteric Fevers, Dysenteries, Infectious Enteritis, Food Infections and Poisonings)

See Chapter XXVII, p. 332, for control among the population. The measures are essentially the same for these diseases :—

A. **Search for the Source and Paths of Infection.**

1. Search for the *article of diet* responsible, *e.g.*, water, milk, ice-cream, raw vegetables, shell-fish.
2. Search for the *place* from which such articles came, *i.e.*, waterworks, dairy, kitchen, shop, oyster-beds, etc.
3. Search for the *person*—the primary source of infection—usually a carrier who is a food handler.

The search frequently involves inquiry outside the hospital where the investigation is the function of the Medical Officer of Health. He should therefore be advised of such outbreaks so that he may collaborate at the earliest possible stage.

B. **Overhaul of the hospital practice** for preventing bowel-to-mouth infections, viz., sanitary disposal of excreta, personal hygiene of nursing and kitchen staff and cleanliness in the preparation of food and drink.

C. **Protection of susceptible contacts** if an efficient agent is available. When a single case appears in a ward and there are reasonable grounds for the belief that the patient was incubating

the disease at the time of admission and that the prospect of transmission to others has been remote, it is usually sufficient to keep contacts under observation for the quarantine period of the disease. In all other cases more extensive measures are necessary. Explosive outbreaks strongly suggest that some common article of diet consumed in the ward is responsible.

I. ENTERIC FEVERS

Outbreaks seldom have their source in hospital, but if they do, measures must be stringent. Any article of diet under suspicion should be excluded from the menu and submitted for bacteriological examination ; in the case of water, chemical analysis is also necessary. Water and milk should be boiled and ice-cream, shell-fish and raw vegetables excluded until it is certain they are not responsible. Carriers who are food handlers are the most likely primary sources of infection, but when investigating, the following procedure is applicable to all patients and staff in the ward, and to the kitchen staff of the hospital :—

(i) Inquiry as to recent alimentary disorders, *e.g.*, diarrhœa, and, if necessary, clinical examination.
(ii) Bacteriological examination of stools and urine.
(iii) Serological examination.

Routine bacteriological examination, particularly of staff, is troublesome and may disorganise the work of the hospital ; serological examination is more easily carried out. It may be sufficient to restrict bacteriological examination to those with a positive Widal reaction and to those with a history of recent alimentary disorder. The significant titres of antibodies are given in Chapter XXX, p. 377. Mention must here be made of Felix's statement that the detection of Vi-antibodies in a suspected carrier is evidence of an existing infection, even if bacteriological examination fails to reveal the typhoid bacillus.

The protection of contacts by active immunisation with T.A.B. is held by some to be contraindicated because of a possible negative phase after the injection, during which susceptibility to the disease is increased. Such a negative phase is largely hypothetical. In the case of contacts of *typhoid* fever, passive immunisation with 10 c.c. of Felix's Vi-serum may be followed immediately, or some days later, by active immunisation.

II. DYSENTERIES

Water is seldom responsible ; milk and other articles of diet should be suspected. The primary source may be another patient or a member of the staff. The general measures and the bacteriological and serological examinations described above may be necessary, but serological examination is not so reliable as in the enteric fevers.

III. INFECTIOUS ENTERITIS OF CHILDREN

Milk is the most likely source of infection and should be boiled. All patients with diarrhœa, however slight, should be isolated. The general measures described in Chapter XXVIII to ensure proper disposal of excreta and asepsis in the preparation of feeds should be rigidly enforced. Children under two years of age should not be admitted to the ward for a week after the last case has been removed.

CONTROL OF OTHER DISEASES

Outbreaks of infectious diseases of the nervous system, viz., poliomyelitis, cerebrospinal fever, and epidemic encephalitis are uncommon in hospitals and can be dealt with on the lines indicated in the general section above and in Table XXV. Smallpox is in a special category, as the Medical Officer of Health should personally deal with the outbreak ; the measures employed are outlined in Chapter XXII, p. 273.

For the means of control of louse-borne diseases see Chapter XXXIV.

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